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Archives of Internal Medicine

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THE BENEFICIAL EFFECTS OF BARIUM CHLORID ON ADAMS-STOKES DISEASE *

REPORT OF THREE CASES

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AND
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It frequently happens in the course of complete heart block that attacks of syncope appear associated with standstill of the ventricles. These are the classical attacks known as the Adams-Stokes syndrome. It appears to be a fact that the severity of the attacks depends on the duration of the ventricular asystole. It has been reported [1] that the subcutaneous injection of epinephrin can do away with such attacks, but as the effect of epinephrin generally lasts a very short time, it does not seem likely that the recurrence of attacks is thus prevented. Epinephrin failed to prevent the reappearance of syncope in one of the cases reported here. However, no method has been proposed so far for dealing directly with these attacks in the sense of diminishing their frequency or preventing them. This has been accomplished in the following three cases by the oral administration of barium chlorid.

The periods of standstill are presumably due to the fact that the ventricles, for the moment, contain no mechanism for initiating stimuli. On account of the existence of complete heart block, they can, of course, receive none from the auricles. It occurred to us, therefore, in complete heart block, to make use of the knowledge gained in animal experiments that calcium or barium tended to increase the irritability of the ventricles as indicated by the development of numerous ectopic ventricular beats or ventricular tachycardia.[2] The same effect has been obtained in the experimental animal as a result of barium chlorid, even when complete heart block is produced by clamping the bundle of His.[3] If this were so,

* From the hospital of the Rockefeller Institute for Medical Research and the medical clinic of the Peter Bent Brigham Hospital.

1. Phear, A. G., and Parkinson, J.: Adrenalin in the Stokes-Adams Syndrome, Lancet **1**:933 (May 13) 1922.

2. Rothberger, C. J., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachycardie durch Accelerausreizung, Arch. f. d. ges. Physiol. **142**:461, 1911.

3. Van Egmond, A. A. J.: Ueber die Wirkung einiger Arzneimittel beim vollständigen Herzblock, Arch. f. d. ges. Physiol. **154**:39, 1913.

the ventricles, because of the increased irritability, either through some new ectopic focus or by the action of barium on the idioventricular pacemaker, would not permit a long pause of inactivity to occur. In three patients suffering from Adams-Stokes disease, whose histories are here reported, the attempt was made to observe whether an effect comparable to the one observed in experiments might be obtained. Accordingly, we decided to administer barium chlorid, in doses of 30 mg., three or four times a day by mouth.

In considering the efficacy of the use of barium in this condition, it is necessary to compare its action with that of other agents commonly employed to relieve states like this. In Case 1, atropin was injected not only without effect, but, on the contrary, it was followed by aggravation of the patient's condition. In the other two cases, its use was without influence. Digitalis in adequate doses was administered in the first case with the view to improving, in a general way, the circulation of this patient. Mild attacks of the syndrome were already present when the first dose was given. During the second day of treatment, the number and severity of the attacks increased decidedly, so that the conclusion was natural that the effect of digitalis was harmful. In the other two cases, the giving of digitalis was without effect. In Case 1, the inhalation of amyl nitrite gave relief temporarily; in the other two cases, it was not used. Epinephrin was given in Cases 2 and 3. In each instance, it was planned in case of need to give epinephrin, 0.5 c.c. (1:1,000 solution), directly into the heart. This was not necessary in Case 2, since the attacks were of short duration, although frequent intramuscular injections were made. For about one hour after intramuscular injections, the patient would remain free from attacks of syncope, but soon afterward he would be liable again to periods of ventricular standstill. Patient 3 suffered from violent attacks: pauses of the heart lasting from three to four minutes were observed. During such a major attack, an electrocardiogram was taken, which showed that the ventricles fibrillated during a period of about two minutes, followed by a period lasting another minute and a half in which the ventricles failed to give rise to any action detectable in the curves. During these long seizures, 0.5 c.c. of epinephrin was injected directly into the heart, and after a few seconds the heart began to beat.

Since the use of these agents did not prevent the recurrence of the attacks, we resorted to the administration of barium chlorid. The effect of its action was striking in all three cases. The attacks, which had persisted until barium chlorid was given, ceased entirely on the day on which it was started. The effect, in Case 1, was extraordinary. Previous to the administration of barium chlorid, the patient's condition had constantly become worse until, on the day on which it was started, he

resembled patients in the status epilepticus. He was passing in and out of attacks of syncope constantly, being conscious only about one-half the time. The day following the giving of barium chlorid, there were no more attacks or long pauses, although complete heart block persisted. Although barium chlorid was given by mouth in doses of 30 mg. three times a day for only two days, he remained free from attacks for some weeks. There was a similar direct relationship between the cessation of attacks and the administration of barium chlorid in the other two cases. All three patients left the hospital free from attacks.

REPORT OF CASES

CASE 1.—B. B., a man, aged 55, was admitted in December, 1916, to Rockefeller Hospital, complaining chiefly of pain across the chest and in the head, fainting spells and "hot flashes." There was nothing of significance in the family history. The patient had suffered from measles when a child, but from no other infectious diseases. In the summer months, he had hay-fever. He complained of no symptoms referable to the circulation before the onset of this illness, and appeared to have been in good health.

The illness for which he came to the hospital began in February, 1914, when his complaint was that there were blue spots before his eyes. These would come on with exercise, such as walking. Dizziness occurred at the same time and disappeared on resting. In 1915, he was free of this complaint. In May, 1914, he fell unconscious on the floor and remained so for a short time. A similar attack occurred next day but none after that. In January, 1914, he began to complain of "flashes of heat" over the body. Such attacks recurred at frequent intervals, once a week or oftener, and lasted a few seconds. In July, 1915, he began to complain of precordial pain, which was constant, severe and persistent. In August, 1914, and again in August, 1915, there were attacks of vomiting of two days' duration. For several years there had been cramps of the calves of the legs, which were worse at night, but which did not appear to bear any relation to exercise. His physician stated that he had noticed pulse rates as slow as 9 a minute, and that, about a year before admission, the rate fluctuated between 120 and 24 a minute. At this time, the rhythm was irregular, about 30 a minute.

The patient was not short of breath, at least, in bed. He was pale but not cyanotic. The eyes were prominent. A positive Graefe sign was present. The tonsils were small and atrophic. The superficial lymph nodes, the thyroid gland, lungs and abdomen, except for the liver, were without abnormality. The heart was enlarged, measuring 3.8 cm. in the fourth space on the right side and 14.5 cm. on the left side in the sixth space. The point of maximal impulse of the apex was in the fifth space, 13 cm. from the middle line. The rate was slow, about 30 a minute. The respirations were irregular, seven long deep breaths being followed by three smaller ones, after which a pause ensued. The liver was not felt, but there was dulness on percussion, to 13.5 cm. below the free border of the ribs. The retinal vessels were tortuous. The urine was normal. The Wassermann reaction was negative. There was no edema. It was clear that the patient was suffering from heart block, and this diagnosis was confirmed on examining the electrocardiograms. The auricles were fibrillating. Because of this fact, atropin, 1.2 mg., was injected subcutaneously. The blood pressure (Dec. 22, 1916) before the injection was 240 systolic and 96 diastolic. Afterward, it fell to 200 systolic and 80 diastolic.

On a subsequent occasion (Jan. 4, 1917), atropin, 2.4 mg., was injected subcutaneously. On this occasion, the blood pressure showed no change. After

the injection of atropin the heart rate did not rise. At that time, the blood pressure reading with a Gaertner tonometer was 160. The difference in height between his brachial and tonometer pressures was about 75 mm., so that the brachial pressure was probably approximately 235 mm., a level about average for him. During the course of the atropin test, the "hot flashes" of which he complained on admission reappeared. When these occurred, there were long intermissions in the pulse. January 9, there were many "hot flashes," one very severe, in which the patient became unconscious. Before these "flashes," there was paleness of the face and neck. The eyes became fixed and the pupils wide. The lids then closed for a short time. When they reopened, it was seen that the eyes were rolled quickly upward and to the right, jerking two or three times. There was twitching at the left corner of the mouth. The attack lasted from ten to fifteen seconds. It was not until asystole had persisted for about eight seconds that the rolling of the eyes took place. The patient was given barium chlorid in doses of 40 mg., three times a day for two days (January 12 and 13). On the morning of January 13, the severe attacks of circulatory disturbance ceased and did not recur. The patient left the hospital, February 9, improved.

The difficulty of arriving at an understanding of the nature of the cardiac mechanism in this case was due to the fact that the ventricular rhythm was irregular. It was for this reason, as well as on account of the slow rate, that the atropin tests were given. These injections failed, however, to bring about an increase in the rate of the ventricles. This failure was in all probability not due to inactivity of the atropin because the other signs of atropin action, such as flushing, dryness and dilatation of the pupils were present. Aside from the minor complaints, such as headache, sleeplessness and anorexia, he suffered, between January 1 and 13, from innumerable syncopal attacks, one of which has been described. Some of these were short, others were counted which lasted as long as sixty seconds, and some were even longer than this. Other attacks were short, coming one directly after another, so that the patient gained the impression that he was having one a minute. In any event as many as five or six were counted in a period of ten minutes. The patient usually anticipated the onset of an attack by feeling a sensation of heat, beginning in his feet and gradually mounting upward. In addition, one observed the alternate ashy grayness and flushing of his face. At the time of the attacks and also later there was pain in the precordium.

The remedies that were used have already been enumerated. The effect of barium chlorid has been stated. An analysis of the electrocardiograms was difficult on account of the many forms of the ventricular complexes. There appeared to be at least two distinct foci for stimulus production in the ventricles. After a long pause, it usually happened that the new rhythm was initiated by an ectopic beat (Fig. 1). For the most part, after a single initial ectopic beat, a return to the usual form was observed. Occasionally, there was a repetition of this beat. The inference that was drawn was that the usual source of stimulus production in the ventricles underwent what may vaguely be called fatigue. The heart then stood still until the ectopic focus stepped in and averted permanent standstill and death, or within a period not too long the rhythm was taken up at the usual sites. One might expect a difference in rate between the rhythm initiated at the usual and at the ectopic foci, but this was not the case.

After returning to his home, the patient began again to have frequent attacks. The suggestion was then made that he take calcium lactate, 1 gm., three times a day. After this treatment was begun, his physician reported that the attacks ceased, that he had no pain, and that his chief complaint was shortness of breath. The pulse rate was 30. Death was sudden, November 10, when the patient was returning to bed after a bowel movement. No necropsy was obtained.

Case 2.—A. S. R., a man, aged 32, who first came under observation, Oct. 15, 1923, gave as the chief complaints, dyspnea on exertion, dizziness and attacks of faintness.

The patient's father and mother were living and well, at the age of 70. He had one sister, aged 43, alive and well. There had been no deaths in the family. His child suffered from asthma, and was sensitive to egg and fish.

The patient had had a severe attack of diphtheria at the age of 4, and was given antitoxin. There was no history of rheumatic fever, chorea, pneumonia, typhoid fever, growing pains, sore throat or tonsillitis. The tonsils had not been operated on. He had always been strong and well. He played a considerable amount of golf.

A year before the patient came under observation, the patient was known to have a normal heart rate. He had been active in athletics, and had been captain of the football team in college. More recently, he had been the local champion golfer. The heart rate, August 7, was about 35. The basal metabolism was —7 per cent. The patient was in good health until nine months before, when he first noticed that he became dyspneic when going up hill and on climbing stairs. Shortly after this, he commenced to have periods of dizziness and, on rare occasions, would lose consciousness for perhaps one or two seconds. These usually occurred after exertion, and before rather than after eating. He became nervous and apprehensive as a result. For many years, he had known that he

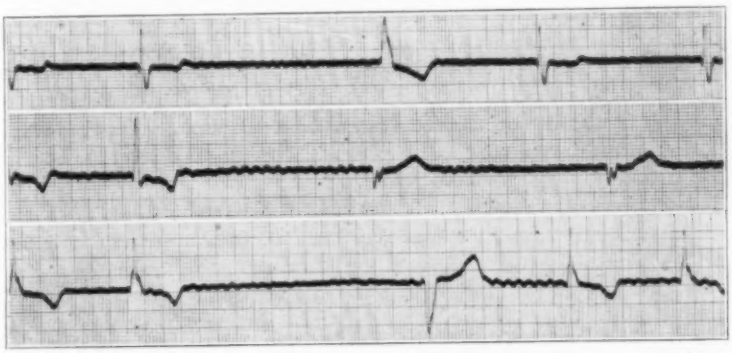

Fig. 1 (Case 1).—Complete auriculoventricular dissociation (complete heart block); fibrillation of auricles in Leads I, II and III. At the beginning of each curve are shown two ventricular beats; then follow long periods of quiescence, the longest being in Lead III and measuring 3.32 seconds. The pauses are interrupted in Leads I and III by a single ectopic contraction and in Lead II by two ectopic contractions. The rate of the ectopic beats shown in Lead II is slower than that of the mechanism usual at this time. The dominant ventricular rhythm is irregular. These curves are interpreted as illustrating failure of impulse formation in the ventricles, the circulation being maintained during failure by the assumption of this function by another focus. This conclusion is adopted after the study of many other curves similar to these taken from this patient. The injection of atropin, on several occasions, failed to alter the degree of block by increasing the ventricular rate; that is to say, irregularity is not due to fibrillation of the auricles, which coexisted. Records exist in which periods of quiescence as long as nineteen seconds were photographed. Still longer ones were observed of which no records were made.

was sensitive to fish, and at times reacted to it with attacks of spasmodic asthma, marked by dyspnea and wheezing, urticaria and edema in the throat. Certain kinds of dust also would occasion attacks of asthma. He found that epinephrin usually gave him relief.

The patient looked somewhat sallow. The pupils were dilated, equal, circular, and reacted normally to light. Both tonsils were enlarged and ragged, but showed no exudate. There was no general glandular enlargement. The lungs showed no dulness, bronchial breathing or râles. On palpation and percussion, the heart was slightly enlarged, measuring 1 cm. outside the nipple line, 12 cm. to the left of the midline. There was no thrill. Auricular beats were definitely heard during the long diastole and, synchronously with these, waves in the veins of the neck were to be seen. The intensity of the first sound at the apex changed occasionally, becoming snapping, muffled or reduplicated. There was a slight systolic murmur at the apex, which was less well heard at the base. There was no diastolic murmur. The heart action was slow and regular, with an occasional lengthening of the diastolic pause. The heart rate was 30 a minute. The blood pressure was 122 systolic and 55 diastolic. The abdomen was negative, except for slight tenderness in the gallbladder region. There was no peripheral edema. The electrocardiograms showed complete heart block with ventricular complexes that indicated defective conduction within the ventricles (Fig. 2). The Wassermann reaction was negative.

In October, 1923, a roentgenogram of the heart, taken at a distance of 7 feet (17.7 cm.), showed moderate cardiac enlargement with no abnormalities in the contour. The measurements were as follows: To the right of the medial line, 5 cm.; to the left, 9.7 cm., and the great vessels, 5.8 cm. The internal diameter of the chest was 26.3 cm. The roentgenograms of the kidney and gallbladder areas showed the kidneys to be apparently normal in size, shape and position. There was no evidence of calculi.

October 18, the urine was yellow, clear and acid. The specific gravity was 1.015. There was no sugar. There was no albumin. The sediment showed no casts, blood or pus.

October 29, in the phenolsulphonephthalein test, 48 per cent. of the drug was excreted in two hours and ten minutes. The vital capacity of the lungs was 4,400 c.c. The weight was 75 kg. The height was 5 feet 9½ inches (176.5 cm.). The systolic blood pressure was 12.8 mm. of mercury; the diastolic, 60.

During his stay of five weeks at the Peter Bent Brigham Hospital, he had no fever. He gained 2.6 kg. in weight. The fluid intake and output were normal. The bowels were normal. The pulse rate was slow, generally ranging from 20 to 35 a minute. October 16, he was given 1 mg. of atropin sulphate subcutaneously, and the heart rate remained constantly at 30 for an hour following the injection. October 17, he was given 2 mg. of atropin sulphate, and the heart rate remained constantly at 29 to 30. October 19, 0.5 c.c. of epinephrin (1:1,000) was given subcutaneously. Following this, the patient felt uneasy and somewhat faint. At this time, the heart rate was 21. During the following hour, the rate rose to 30 and 34.

A few days after his admission to the hospital, long pauses began to interrupt the usual rhythm. At the same time, attacks of dizziness or complete loss of consciousness occurred. Pauses of from five to ten seconds and occasionally of from twelve to fifteen seconds were frequently noted (Fig. 3). The patient became very apprehensive, and the situation somewhat critical. It was found that preceding these spells, for a period of about half an hour, the pulse would be 20 or 22, rather than 30, and even with this slow rate, sudden pauses of about four seconds were frequent. If epinephrin (1:1,000) in doses of from 0.3 to 0.5 c.c. was given subcutaneously, the pulse rate would promptly rise and the dizziness disappear. Five or ten minutes after the injection, the patient would notice that his heart was pounding more rapidly, and he would become slightly nervous and warm. Epinephrin was frequently given, and the administration appeared to prevent impending attacks of syncope, which seemed otherwise to accompany the long pauses of the heart beat. Because there would be slower absorption of the subcutaneous injection during a long

pause of the heart, it was planned to inject epinephrin directly into the heart, if the pause lasted more than thirty seconds. For this purpose, a hypodermic of epinephrin was kept constantly at the bedside.

October 21, the patient had slight convulsions in one of the attacks of unconsciousness. A pause of ten seconds was noted. During the next few days, the patient had frequent attacks, five or ten times a day, which varied in

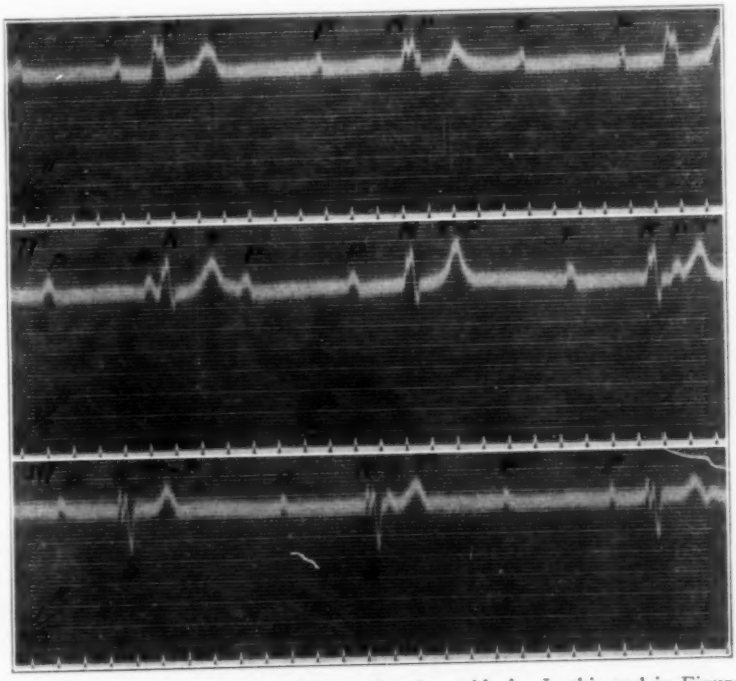

Fig. 2 (Case 2).—Oct. 15, 1923, complete heart block. In this and in Figure 4 are shown Leads I, II and III. The time is marked below in one-fifth seconds. The auricular rate is 75 and the ventricular, 30.

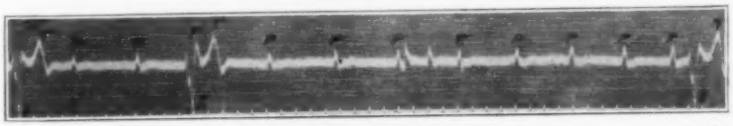

Fig. 3 (Case 2).—October 17, Lead III. This curve shows a ventricular pause of about seven seconds; the auricles continue to beat at a rate of about 79.

intensity, the lighter ones being associated with a feeling of faintness, the more severe ones being accompanied by convulsions. He was receiving frequent doses of epinephrin during this time.

October 24, he commenced to take barium chlorid, 30 mg., by mouth, four times a day, followed in half an hour by subcutaneous injections of 0.3 c.c. of epinephrin. On this day, he had no attack, but he occasionally felt slightly

dizzy. This was the first occasion on which he had had no long pauses of the heart beat for the duration of a week. The next day, he was again free from attacks, and his general condition improved very strikingly. He was propped up in bed, and was able to feed himself. Previous to this, he had been afraid to move for fear of precipitating an attack.

October 26, the dose of epinephrin was reduced from 0.3 c.c. four times a day to 0.2 c.c. four times a day. He had no attacks, October 27. October 28, the dose of barium chlorid was diminished to 15 mg., four times a day, followed in half an hour by 0.2 c.c. of epinephrin. He had no attacks on this day or on the 29th.

October 30, he had one attack of faintness at 8:10 a. m., during which there was a pause of 6 seconds. Epinephrin was given immediately after this attack, but was omitted during the rest of the day. He had no attacks for the next two days. November 1, he received neither barium nor epinephrin. The next day, he was allowed to sit in a chair for fifteen minutes. This occasioned him no discomfort. He had no attacks on this and the two following days. November 5, the effect of an epinephrin nasal spray, 1:1,000, was tried. This produced a burning sensation in the nostrils, but no appreciable change in the heart rate.

November 6, it was decided to try the effect of full doses of digitalis, and digitalis leaves, 0.1 gm., was given four times a day from November 6 to 12; 2.6 gm. in all were given. This did not seem to influence the rate, which remained at about 30. From the time he was allowed to sit in a chair, the patient's activities were greatly increased, and finally he walked around the ward without discomfort. He had no further attacks during his stay in the hospital, has remained in excellent health for more than a year since his discharge, and is doing his ordinary work in an insurance business. He has taken no barium since leaving the hospital and the complete heart block has persisted.

The diagnosis was Adams-Stokes syndrome, complete heart block and chronic myocarditis.

It seems rather striking that the attacks of unconsciousness and convulsions ceased abruptly the day he commenced to take barium chlorid, for they occurred frequently up to October 24. From then on, he had only one slight attack. Atropin did not relieve the complete heart block. Epinephrin always increased the ventricular rate slightly, but this was temporary. Full doses of digitalis seemed to have no appreciable effect on the mechanism of the heart beat.

Case 3.—A. T. H., a woman, aged 52, a school teacher, who was admitted to the Peter Bent Brigham Hospital, Dec. 31, 1923, complained chiefly of attacks of unconsciousness.

There was nothing of significance in the family history.

The patient had had scarlet fever at the age of 4. Following this, she had had trouble with the left ear and gradually lost hearing on that side. Ten years before, the right ear gradually became deaf. She had had diphtheria twice, at the ages of 6 and 7. There was some question as to the presence of paralysis of the leg muscles, at the time of the attacks of diphtheria. Following the second attack, she was unable to be up and around for about one year. She had had tonsillitis at the age of 22. For about fifteen years, and continuing to four years before, she has experienced, at irregular intervals, frequent attacks of pain in the epigastrium, so severe as to require morphin for their relief. The general nature of these attacks resembled gallstone colic.

For the last year, the patient has become increasingly short of breath and had had palpitation on exertion. One year before admission, she suddenly fainted and fell to the floor. She was unconscious for about five minutes. Similar attacks had occurred frequently since then. She could usually tell a few minutes before when an attack was coming on. At times she almost lost consciousness but regained control of herself. Her sister, who was a nurse,

had frequently tried to take her pulse during a spell but had been unable to feel it. After an attack, the rate was usually about 30. While she was unconscious, her muscles contracted convulsively. The day before her first admission to the hospital, she lost control of her bowels and bladder during an attack. This was the first time that this had occurred. The attacks might occur as often as twice a day, or there might be periods of two or three weeks in which she was entirely free from them.

The height was 153 cm. The weight was 76 kg. The surface area measured 1.74 sq. mg. The patient was a well developed, somewhat obese, middle-aged woman. She lay comfortably in bed in a semirecumbent position. The pupils reacted normally. There was no glandular enlargement. The throat showed no abnormality. The left ear was totally deaf. The patient could hear with the right ear only with the aid of an electrical apparatus. The lungs were clear, there being neither bronchial breathing, dulness or râles. The vital capacity of the lungs was 2,300 c.c. January 4, a roentgen-ray examination

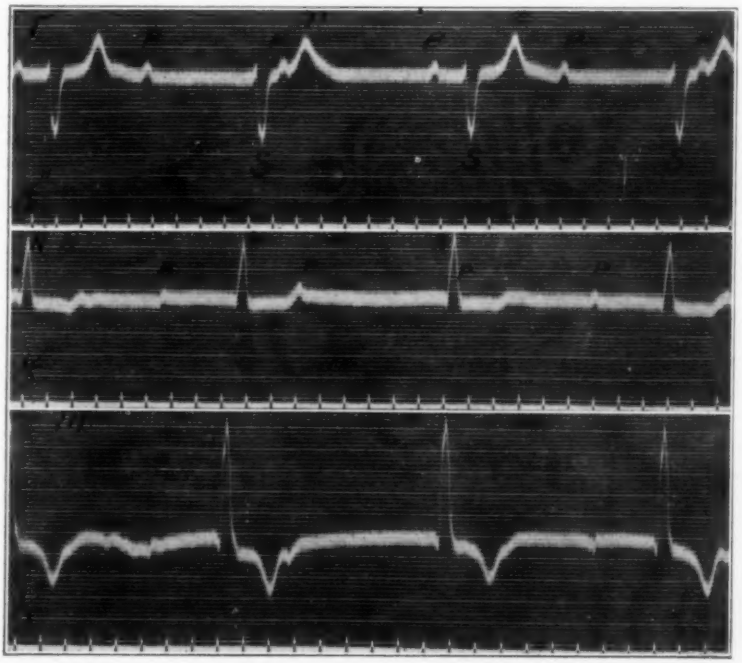

Fig. 4 (Case 3).—Jan. 23, 1924, complete heart block. The auricular rate is 50 and the ventricular, 35.

of the chest, with the patient in bed, showed marked cardiac enlargement. The lungs appeared mottled. The apex impulse of the heart was seen and felt 13 cm. to the left of the midsternal line. The supracardiac dulness in the first space measured 7 cm. There was no thrill at either the apex or the base. The heart rate was slow and irregular, being about 30 a minute. The quality of the first sound changed in different cycles. There was a fairly loud systolic murmur at the apex and a louder and harsher one in the aortic area. There

was no diastolic murmur to be heard. Distinct auricular waves were to be seen in the veins of the neck during the long pauses of the heart. Pressure of the left and right vagus nerves produced no effect on the heart. The Wassermann reaction was negative.

An examination of the stools showed nothing significant. There was no sign of occult bleeding. In the phenolsulphonephthalein test, 55 per cent. of the drug was excreted. The urine was clear and acid. The specific gravity was 1.016. There was a slight trace of albumin. There was no sugar. The sediment showed a rare hyaline cast. The hemoglobin was 100 per cent. The red blood cell count was 5,056,000. The white blood cell count was 9,880. A stained smear showed a normal differential count. The erythrocytes appeared normal. The electrocardiograms showed complete heart block (Fig. 4).

On the evening of her admission to the hospital, the patient suffered from an attack of unconsciousness at 6 p. m. She gave a slight groan; her arms and legs became stiff, and her breathing ceased. No pulse could be obtained, and no heart sounds could be heard over the precordium for about twenty seconds. Then the heart suddenly began to beat slowly, and almost immediately respiration began. She then turned her head and was able to speak. Jan. 1, 1924, she was given 1 mg. of atropin subcutaneously. This caused no change in the mechanism of the heart beat. Later the same day, she was given 2 mg. of atropin. This dose also was without effect. During the next three days, a total of 1.9 gm. of digitalis leaves was given by mouth which caused no appreciable change in the heart. January 8, a second attack of unconsciousness occurred similar to the first. Following this she became apprehensive and feared another attack; the fear may however have been due to the fact that the heart rate was slower than usual, about 25 a minute.

On the morning of January 13, a third attack occurred. She first turned pale, then uttered a cry and turned her head backward. The eyes were seen to roll up. In a few seconds, she became cyanotic and continued to moan. From the commencement of the attack, no pulse could be felt at the wrist. No heart sounds could be heard over the precordium with a stethoscope. She was immediately given 1 c.c. of epinephrin intramuscularly, and after a standstill for about half a minute, the heart began to contract slowly for 4 or 5 beats, and then gradually accelerated its rate until, in about ten seconds, it was 140. One minute later, the rate was 72, and in another minute, 64. Within three minutes of the onset of the attack, she was conscious again and complained only of exhaustion. The heart then gradually slowed to a rate of 40. There was then coupled rhythm. January 14, a milder attack of unconsciousness occurred. January 15, she commenced to take barium chlorid, 30 mg., by mouth three times a day. Following the administration of this drug, there were no attacks until February 3, when she was discharged from the hospital. January 24, barium chlorid was omitted. In its stead, 5 c.c. of physiologic sodium chlorid solution, three times a day, was administered.

February 3, when the patient was discharged from the hospital, she was advised to continue taking barium chlorid, 30 mg., three times a day. She continued to do this for ten days and felt well, except for an occasional feeling of faintness. She was up and about and able to walk two blocks. Finally, she was persuaded to give up medicine by a Christian science healer. Then she noticed a slow, irregular pounding of the heart. February 23, she had a severe attack and was unconscious for three or four minutes. During the next few days, she had from four to six attacks of unconsciousness each day. The day before her second admission to the hospital, she had six attacks between 2 a. m. and 7 p. m. These were characterized by a large, booming sensation in her left chest, followed by a number of similar "vibrations" of her heart. She was able to call for assistance, and then suddenly was unable to breathe and lost consciousness. She then began to struggle and to twitch all over, often biting

her tongue and becoming incontinent of urine and feces. The spells of unconsciousness lasted from three to five minutes, and when she recovered she had a sensation of water running in her ears and a bitter taste in her mouth. Her sister, who observed these spells, stated stated that no pulse could be felt for half a minute or more. On recovery, the patient was greatly excited.

The physical examination at the time of the second admission resembled the first. During the first few days, the patient had four attacks of unconsciousness. In two of these, the heart stopped completely for half a minute and this pause was followed by a slow rate; in two, the standstill of the heart was followed by tachycardia with a heart rate of 160. At the time of each attack, 1 c.c. of epinephrin (1:1,000) was given intramuscularly. What epinephrin had to do with the cessation of the attacks is uncertain, for at the time of the injection the patient was unconscious and pulseless. It is doubtful whether absorption could take place under such circumstances. During the succeeding days, between March 8 and 14, the heart beat was frequently in coupled rhythm, and the patient occasionally complained of palpitation. On the evening of March 13, at 10 p. m., a short attack of unconsciousness without convulsions occurred.

On the morning of March 14, she commenced to have another attack. She was immediately given 1 c.c. of epinephrin intramuscularly. For four minutes, between 8:15 and 8:19, no beats were heard at the apex, and no pulse was felt at the wrist. At 8:19 the heart began to beat at a rate of 135. At 8:23 the rate had fallen to 41. The respirations were then 23. The patient's color gradually returned, and she began to regain consciousness at 8:27. At 10:30 another attack was observed, during which she was pulseless and no heart beats could be heard for three minutes. During this spell, there was frothing of the mouth, cyanosis and incontinence of urine. As this attack passed off, there was convulsive straightening of the arms and legs just before the radial pulse became perceptible. Immediately after the standstill of the heart, the rate was 160; seven minutes later, it was 41. On this day, she commenced to take barium chlorid by mouth, 30 mg., four times a day. On the evening of March 4, there were two slight attacks at 8 and 10 p. m. There were no further attacks during her stay in the hospital, and the patient steadily improved until her discharge from the hospital, April 27. Barium chlorid was omitted, March 21.

March 14, during the most violent attacks of complete standstill, epinephrin was administered frequently. During two of the longer spells, 0.5 c.c. was injected directly into the heart. It seemed unlikely that spontaneous contraction would begin for, since the circulation was stationary, it seemed doubtful whether epinephrin injected into the skin would be absorbed. The patient continued to take barium chlorid by mouth for seven days after leaving the hospital, and continued in fair condition. May 28, she died suddenly. Previous to this, she had been taking barium chlorid irregularly, and for several days before her death she took thyroid tablets, 1 grain (0.06 gm.) three times a day.

The diagnosis was Adams-Stokes syndrome, complete heart block and gallstones.

SUMMARY

In three patients with complete heart block suffering from frequent attacks of syncope and convulsions (Adams-Stokes syndrome), the customary therapeutic procedures, including epinephrin, did not prevent the recurrence of attacks, whereas barium chlorid given by mouth, in each instance, promptly proved successful in rendering the

patients free from attacks. The action of barium served to increase the irritability of the ventricles and to prevent the long asystolic periods that occurred in this condition. These successes warrant the trial of barium chlorid when the recurrence of attacks of Adams-Stokes syncope are frequent.

LEUKEMIA

THE RELATIVE VALUES OF CELL MORPHOLOGY AND THE PEROXYDASE REACTION AS DIAGNOSTIC AIDS *

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The demonstration of oxydase and peroxydase ferments [1] in certain cells of bone marrow origin has led to the extensive application of these reactions as diagnostic aids in the differentiation of myeloid and lymphoid leukemia. This is particularly true of the acute leukemias, in which undifferentiated progenitors of the granular and nongranular leukocytes form a conspicuous part of the blood picture.

The popularity of the oxydase reaction is largely due to its supposed ability to distinguish, by simple color reactions, primitive blood cells which, by the ordinary methods of staining, are exceedingly difficult, if not impossible, to differentiate. The diagnostic value of the reaction in a given case naturally depends on its specificity for the cells in question, a point on which there is considerable difference of opinion.

To those hematologists who regard the oxydase reaction as specific for myeloid cells, the presence of these ferments represents a biochemical difference by which they differ from cells of lymphatic origin. Thus, Naegeli,[2] Schridde,[3] and other adherents of the dualistic theory regard it as an important argument favoring the complete separation of the myeloid and lymphoid systems. Schultze,[4] Peters,[5] Herxheimer,[6] Marchand,[7] Meyer [8] and others described oxydases in nongranular "myeloblasts." That lymphocytes may react similarly is denied.

Other observers, however, have failed to see in the oxydase reaction a certain method of cell identification. While the presence of ferments

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1. The nature of the causative elements in the reactions described will not be discussed. For purposes of convenience, they are referred to as ferments.

2. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, 1923.

3. Schridde, H.: Die blutbereitenden Organe, in Aschoff's Pathologische Anatomie, Ed. 6, Jena, **2**, 1923.

4. Schultze, W. H.: Die Oxydasereaktion an Gewebsschnitten und ihre Bedeutung für die Pathologie, Zugleich ein Beitrag zur Differentialdiagnose der Leukämieen, Beitr. z. path. Anat. u. z. allg. Path. **45**:127, 1909.

5. Peters, Jacob: Ein Beitrag zur Leukämiefrage, München. med. Wchnschr. **56**:1478, 1909.

6. Herxheimer, G.: Ueber einen kombinierten Fall von lymphatischer und Myeloblastenleukämie, Centralbl. f. allg. Path. u. path. Anat. **24**:897, 1913.

7. Marchand: Ueber akute Myeloblastenleukämie, München. med. Wchnschr. **58**:924, 1911.

8. Meyer, Oskar: Zwei Fälle akuter Myeloblastenleukämie, zugleich ein Beitrag zur Frage der Sog. Leukanämie, Frankfurt. Ztschr. f. Path. **15**:40, 1914.

in the granular leukocytes and their immediate precursors (myelocytes) is admitted, their constancy in the still earlier nongranular forms ("myeloblasts" of the dualists and "hemocytoblasts" or "lymphoidocytes" of the unitarians) is questioned. Dunn [9] and Jochmann and Blühdorn,[10] among others, described myeloblastic leukemia in which the myeloblasts failed to react. Jolly [11] states that "myeloblasts" always react negatively. Rosenthal [12] likewise found that primitive cells contained no oxydase ferments unless granules (specific or azurophilic) were present. Instances in which "myeloblasts" do not contain oxydases are ascribed by the dualists to pathologic loss of the ferments.[13] The specificity of oxydases is further questioned by Menten,[14] who found them in many cells, including lymphocytes.

Peroxydases are generally regarded as of the same significance as the oxydase ferments, though results obtained by one method cannot be assumed of another. Variations in technical procedures used to demonstrate ferments may partially explain the conflicting results in the literature. That certain methods demonstrate more oxydase containing cells than others has been frequently noted.

The data presented in this paper were obtained by the use of a benzidin peroxydase stain [15] and controlled by duplicate smears prepared with Jenner-Giemsa or Wright's stains. The peroxydase solution is of the following composition: 80 per cent. methyl alcohol, 25.0; benzidin, C.P., 0.1, and hydrogen peroxid, 2 drops.

The solution is poured over the blood smears and, after a minute, is diluted with an equal amount of distilled water. This is allowed to remain for five minutes, after which it is poured off, the slide washed with distilled water, and counterstained by Jenner-Giemsa or Wright's method. There is a distinct advantage in counterstaining with the same stain used in ordinary differential counts, as all structures that do not contain peroxydases are stained as usual, and may be easily identified.

With this method, I have, in a routine manner, performed the peroxydase reaction in a series of leukemic and nonleukemic condi-

9. Dunn, J. S.: The Use of the Oxydase Reaction in the Differentiation of Acute Leukaemias, Quart. J. Med. **6**:293, 1913.

10. Jochmann and Blühdorn: Ueber akute Myeloblastenleukämie, Folia haematol. **12**:181, 1911.

11. Jolly, J.: Traite technique d'hematologie, morphologie, histogenese, histophysiologie, histopathologie, Paris, 1923, pp. 379 and 955.

12. Rosenthal, N.: Studies on the Oxydase Reaction of the Cells in Normal and Leukemic Blood, Arch. Int. Med. **20**:184 (Aug.) 1917.

13. Von Jagić and Neukirch: Ueber das Auftreten grosser mononucleärer ungranulierter Zellen im Blute chronischer Myelämien, Berl. klin. Wchnschr. **47**:874, 1910.

14. Menten, Maud L.: A Study of the Oxydase Reaction with Alpha-Naphthol and Paraphenylendiamin, J. M. Res. **40**:433 (Sept.) 1919.

15. McJunkin, F. A.: A Benzidin-Polychrome Stain for Blood, J. A. M. A. **74**:17 (Jan. 3) 1920.

tions, and have obtained results that are at variance with the prevalent opinion regarding its value as a diagnostic procedure.

STAINING REACTIONS OF LEUKOCYTE GRANULES

In slides stained by the peroxydase method, a positive reaction is indicated by the presence of brownish or bluish granules in the cytoplasm of the cells. If granules that do not react positively are present, they may be demonstrated by suitable counterstains.

The relation of ferments to the cytoplasmic granules is disputed. Naegeli and many others believe that certain nongranular cells react positively. According to Pappenheim,[16] the reacting substances are in the cytoplasm, but not in the granules. The reaction appears, however, to be confined to the cytoplasmic granules, conforming to the latter in size and shape. Panton, Tidy and Pearson [17] and Rosenthal [12] have likewise considered the granules as the bearers of the reacting substances.

In normal blood, the neutrophil and eosinophil granules react positively for peroxydases, the latter more rapidly and strongly than the former. Those monocytes which contain azurophilic granules also react, though less intensely. The statement of Naegeli that monocytes react with the same intensity as the neutrophils is not confirmed. Rosenthal found considerable differences in the reactions of monocytes. Sabrazès [18] found that monocytes with round nuclei contained no ferments, while those with lobulated nuclei reacted positively. Panton, Tidy and Pearson found them to react only when azurophilic granules were present.

If the preparation is counterstained, it is observed that the basophilic granules are stained thereby, but that they contain no peroxydase. Graham's [19] results were similar, though Naegeli [2] and Pappenheim [16] describe positive reactions in basophils. Dunn,[20] using an oxydase method, found the basophils to react less strongly than the granules of other cells. Rosenthal found them to react for oxydases, but not for peroxydases.

No ferments were demonstrated in the azure granules of lymphocytes or of blood platelets.

Peroxydases were never present in nuclei, nor were they found in the basophilic substances (polychromasia and basophilic stippling) of erythrocytes.

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16. Pappenheim, A.: Morphologische Hämatologie,' Leipzig, **2**, 1919.
17. Panton, Tidy and Pearson: The Leukaemias: An Analysis of Fifty-Nine Consecutive Cases, Quart. J. M. **7**:340, 1914.
18. Sabrazès, J.: Des oxydases et peroxydases du sang, Arch. d. mal. du coeur **15**:841, 1922.
19. Graham, G. S.: The Hemic Basophil, J. Exper. Med. **31**:209 (Feb.) 1920.
20. Dunn, J. S.: The Oxydase Reaction in Myeloid Tissues, J. Path. & Bacteriol. **15**:20, 1911.

In leukemic blood, the immature cells contain types of granules other than those already mentioned.

Certain of the immature cells contain granules stainable by azure-eosin mixtures, that differ from the azure granules found in normal lymphocytes and monocytes. Theories regarding the significance of these granules have led to considerable discussion.

Naegeli describes them as "unripe" neutrophilic granules, and terms the cell that contains them "promyelocyte." Their nongranular predecessor is the "myeloblast."

Ferrata [21] believes that they indicate an early stage in myeloid differentiation. He recognizes two varieties, a small type indicating the first stage of neutrophil granulogenesis ("proneutrophil" granules), and a larger type as the forerunners of the eosinophils ("proeosinophil" granules). These granules later disappear, their place being taken by the specific granulation. In Ferrata's terminology, these cells are the "myeloblasts" (proneutrophilic or proeosinophilic), which are derived from the nongranular "hemocytoblast." The "myeloblast" of Naegeli is therefore morphologically identical with the "hemocytoblast" of Ferrata; the "promyelocyte" or Naegeli, with the "myeloblast" of Ferrata.

According to Pappenheim [16] and Jolly,[22] these azure granules are of no diagnostic import, are inconstant in their appearance, and may be present in either myeloid or lymphoid cells.

When the peroxydase reaction is applied to cells containing these granules, they react positively. This is amply confirmed by control specimens in which the percentage of cells is calculated as indicated in the method given below. Furthermore, the counterstain fails to demonstrate any granules that do not react, though the azure granules of lymphocytes are clearly stained. It is necessary, of course, to use a counterstain containing azure and eosin, such as Wright or Giemsa stain. In azurophilic bodies of abnormal form (such as the rod-shaped Auer bodies), the ferment is confined to the rod itself.[23] These rods probably occur only in myeloblasts in acute myelogenous leukemia.

It seems logical to conclude, therefore, that the azurophilic granules of immature cells indicate differentiation toward myelocytes. I have therefore followed Ferrata's nomenclature in classifying them and refer to them as "myeloblasts."

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21. Ferrata, A.: Einige neue Feststellungen über die Vorstufen der Granulozyten, Folia haematol. **9**:549, 1910; Le Emopatie, Milan, **1**, 1918.

22. Jolly (Footnote 11, pp. 222 and 977).

23. Rosenthal (Footnote 11). Ishikawa, T.: Ueber den Auerkorper bei einen Falle von akuter Myeloblastenleukamie, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1919. Richter, M. N.: The Presence of Auer Bodies in Leukemic Tissues, Arch. Int. Med. **31**:677 (May) 1923.

As noted above, Ferrata described a large type of granule as the forerunner of the eosinophil. This variety occurred so infrequently that no conclusions regarding its nature or peroxydase reaction can be drawn here. Many eosinophil myelocytes, however, contained varying numbers of basophil granules. These differed from Ferrata's "proeosinophil" granulation in being basophilic rather than azurophilic. Graham [19] considers these as degenerate eosinophils. Downey,[24] however, regards them as immature eosinophil granules. Jordan and Speidel [25] have found them in lower forms, and conclude that they represent a phylogenetically and ontogenetically early stage of eosinophil granulogenesis.

With the peroxydase solution, these granules fail to react, though the eosinophil granules of the same cell react strongly. They are the only negatively reacting granules that were found in cells containing peroxydases.

It is possible that the monocytes also have an immature form of granulation. In a case of acute myelogenous leukemia with associated anemia of the primary type (so-called leukanemia), I have observed immature monocytes (monoblasts) with azure granules slightly larger than normal, which failed to react for peroxydases.

In the series of cases here reported, the nongranular primitive cells (hemocytoblasts) have always reacted negatively.

PEROXYDASE PERCENTAGES IN LEUKEMIA

The data concerning the peroxydase reaction of leukocytic granules reported above may be confirmed by comparing the percentage of peroxydase containing cells with the sum of the percentages of those cells which contain granules of the types thought to react positively, as determined from control specimens prepared by suitable methods. It will be found that, in good preparations, the calculated and observed results agree within the limits of error in counting. In the present series, cover slip preparations were used exclusively, as it is believed that the distribution of cells is more uniform, especially in cases with low total leukocyte counts. The stains used were either Wright or Jenner-Giemsa.[26]

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24. Downey, Hal: Heteroplastic Development of Eosinophil Leukocytes and of Hematogenous Mast Cells in Bone Marrow of Guinea-Pigs, Anat. Record **8**:135, 1914.

25. Jordan, H. E., and Speidel, C. C.: Studies on Lymphocytes, III, Granulocytopoiesis in the Salamander, with Special Reference to the Monophyletic Theory of Blood Cell Origin, Am. J. Anat. **33**:485 (July) 1924.

26. The smear should be covered with Jenner's stain for three minutes; then an equal amount of distilled water should be added and let stand for one minute. This should be poured off and, no washing being done, diluted Giemsa stain (1 drop to 1 c.c. of distilled water) should be added and let stain for from ten to fifteen minutes. The smear should then be washed in distilled water, dried, and mounted in neutral balsam or euparol.

The importance of using a good polychrome stain will be discussed later.

Leukemic blood varies considerably in the relative proportions of undifferentiated and partially differentiated cells which it contains. As a rule, the chronic leukemias contain a relatively large number of the latter type, while the acute leukemias contain large proportions of undifferentiated cells (hemocytoblasts).

As the hemocytoblasts contain no peroxydases, while these ferments are present in granular myelocytes, the percentage of reacting cells in cases of myeloid leukemia depends on the relative number of each type which is a very variable quantity.

The examples of actual counts recorded in the accompanying tables are of interest in that they illustrate the close agreement of the calculated and observed results of the peroxydase reaction. The terminology used in classifying the cells is that of Ferrata.

TABLE 1.—*Chronic Myeloid Leukemia*

	Leukocytes, 150,000 Per Cent.
Hemocytoblasts	33
Promyelocytes, neutrophilic	3
Promyelocytes, eosinophilic	1
Myelocytes, neutrophilic	2
Polymorphonuclear neutrophils	33
Lymphocytes	23
Rieder cells (with azurophil granules)	5
Megakaryocytes	2

Peroxydase percentage: calculated, 44%; observed, 42%.

The differential count presented in Table 1, from a case of chronic myelogenous leukemia, contains a variety of mature and immature cells of which all except the hemocytoblasts, lymphocytes and megakaryocytes contained granules of the peroxydase type. Adding their percentages, we would expect to find 44 per cent. positively reaching cells. Actual count showed 42 per cent.

The course of this case was followed for several months, during which time the blood count varied considerably. At a later date, the differential count was that shown in Table 2.

The principal change is in the reduction in the number of the hemocytoblasts. The myeloblasts in this classification contain azurophil granules, and react positively. The hemohistioblasts were undifferentiated, and contained no granules. It has been shown that the peroxydase reaction in hemohistioblasts is negative unless granules are present.[27]

27. Richter, M. N.: Observations on the Hemohistioblast of Ferrata, Am. J. M. Sc. **169**:336 (March) 1925.

From the count in Table 2, we would expect to find 59 per cent. reacting cells. Actual count showed 61 per cent.

The case of acute myelogenous leukemia presented in Table 3 is of interest in that it contains a large percentage of negatively reacting cells (mainly hemocytoblasts). The plasma cells, which appear in small numbers in many conditions, are usually nongranular as they appear in the blood stream, though they may contain cytoplasmic granules in the

TABLE 2.—*Chronic Myeloid Leukemia*

	Leukocytes, 110,000 Per Cent.
Hemohistioblasts	2
Hemocytoblasts	9
Myeloblasts	14
Promyelocytes, neutrophilic	5
Myelocytes, neutrophilic	9
Metamyelocytes	18
Polymorphonuclear neutrophils	9
Lymphocytes	18
Monocytes (with granules)	4
Monocytes (without granules)	9
Rieder cells (without granules)	3
Peroxydase percentage: calculated, 59%; observed, 61%.	

TABLE 3.—*Acute Myelogenous Leukemia*

	Leukocytes, 63,800 Per Cent.
Hemocytoblasts	75.0
Myeloblasts	0.5
Promyelocytes, neutrophilic	2.5
Myelocytes, neutrophilic	1.0
Myelocytes, eosinophilic	0.5
Metamyelocytes	3.0
Polymorphonuclear neutrophils	1.0
Lymphocytes	12.5
Monocytes (with granules)	1.5
Rieder cells (with granules)	2.0
Plasma cells	0.5
Peroxydase percentage: calculated, 12%; observed, 13%.	

tissues.[28] The writer has shown [29] that one variety of granule (Russell's fuchsin body) gives a positive peroxydase reaction.

COMMENT

The clinical value of the peroxydase reaction depends on its specificity and the degree of accuracy with which positively or negatively reacting cells may be identified.

28. Dubreuil, G., and Favre, M.: Cellules plasmatiques, Plasmazellen à granulations speécifiques, Cellules à corps de Russell (Cytologie et formes évolutives), Arch. d'anat. micr. **17**:302, 1920-1921.

29. Richter (Footnote 23, third reference).

As indicated in the foregoing observations, a positive reaction indicates the presence of cells of the granulocytic series,[30] while a negative reaction does not necessarily indicate their absence.

Many of the early workers on oxydases reported them in nongranular cells that were thought to be of myeloid origin ("myeloblasts" of Naegeli). Probably some of the confusion is due to variations in technic. As has been noted, different results are obtained by varying the methods of demonstrating ferments. There is, however, another source of error, the variations in the staining technic of the control specimens.

Thus, Dunn, using Jenner's stain as a control, reported that, in a fetus of three and one-half months gestation, a certain percentage of the nongranular cells reacted positively for oxydases. He concludes that "these cells were without doubt the nongranular mother cells of the myelocytes, and it was evident that in them the appearance of the oxydases had preceded recognizable granule formation." Schultze [4] reported oxydases in cells that contained no granules, by Ehrlich's staining method. Neither Jenner's nor Ehrlich's solutions contain methylene azure, which is essential for the staining of the azurophilic granules. The conclusions of Dunn and of Schultze that the cells in question were nongranular may therefore be questioned, as their methods were inadequate for granule demonstration.

At a later date, Dunn [9] observed that the oxydase reaction is negative in the more early forms of marrow cells, and that, when positive, it is associated with changes that are recognizable by the ordinary methods of staining.

Panton, Tidy and Pearson [17] controlled their preparations with Leishman's stain, which demonstrates azure granules, and concluded that the nongranular "myeloblasts" do not contain oxydases. Rosenthal used Jenner-Giemsa stain and obtained the same results.

Chosrojeff [31] reported a case of myeloblastic leukemia in which great reliance was placed on the results of the oxydase reaction. As many of the "pathologic lymphocytes" (myeloblasts) contained the typical myeloid azurophil granulations, the positive oxydase reaction should be expected. According to my view regarding the significance of these granules, the correct diagnosis could have been made from morphologic studies alone.

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30. Myeloblast to granulocyte. The reaction indicates cell type, but not necessarily the tissue of cell origin. The significance of peroxydases in monocytes is uncertain, as these cells probably arise in more than one tissue.

31. Chosrojeff, G. P.: Myelosis Aleucaemica Acuta Micromyeloblastica, Folia haematol. **20**:33, 1915.

Fiessinger and Roudowska [32] reported positive oxydase reactions in nongranular cells, but, at a later date, Fiessinger and Broussolle [33] found them to react negatively.

In the cases of Marchand,[7] Meyer [8] and others, the staining technic for the controls is not given.

As it is necessary to employ proper technic for staining control smears, this is even more important in controlling sections of organs. Kwasniewski,[34] for example, found that the results of the oxydase reaction on blood smears did not always correspond to the results obtained on sections in the same case. It is exceedingly difficult, frequently impossible, to establish that cells in the control tissue sections contain no granules. It is usually better to use, as controls, tissue smears or imprints stained by a suitable method.[35]

Cases comparable to those of other writers, in which peroxydase containing cells were devoid of all granules in suitably stained controls were not encountered. In the cases observed by me, the peroxydase reaction has yielded no information that could not be obtained from well prepared blood smears stained by a suitable polychrome method.

To be sure, cases of chronic myelogenous leukemia have a high percentage of reacting cells; but chronic myelogenous leukemia is sufficiently easy of diagnosis from ordinary slides. It is in the acute leukemias, in which the primitive nongranular forms predominate (sometimes forming more than 90 per cent. of the total leukocytes), that the peroxydase reaction is resorted to, and, in my experience, it is in just these cases that it fails to add data of diagnostic importance.

Careful examination of the preparations reveals the fact that the nongranular elements of both myelogenous and lymphatic leukemia, in both chronic and acute forms, react negatively for peroxydases. The percentage of these cells may be counted in the counterstained peroxydase preparations just as accurately as in the controls, as they appear the same in both. If, therefore, these elements constitute a considerable

32. Fiessinger and Roudowska: La réaction microchimique des oxydases dans les tissus humains, Arch de méd. expér. et d'anat. path. **24**:585, 1912.

33. Fiessinger, N., and Broussolle, J.: Etude biologique de la cellule indifférenciée des lucémies aigues, Bull. et mém. Soc. méd. d. hôp. Paris **45**:211 (Feb. 18) 1921.

34. Kwasniewski: Ein Beitrag zur Klinik und Histogenese der akuten Myleoblastenleukämie, Deutsch. Arch. f. klin. Med. **145**:83, 1924.

35. Ferrata's modification of the Jenner-Giemsa method for tissue smears is as follows: The smears should be dried in air for at least ten minutes; then covered with Jenner's stain for from eight to ten minutes. The Jenner's stain should be diluted with twice its volume of distilled water for three minutes. This should be poured off and diluted Giemsa stain (2 drops to 1 c.c. of distilled water) should be added and let stand for at least fifteen minutes. The smear should then be washed in distilled water, dried and mounted in neutral balsam.

proportion of the total, their negative reaction may lead to an erroneous diagnosis of lymphatic leukemia.

These observations admit of wider biologic application. The question concerning the identity or nonidentity of the stem cells of the myeloid and lymphoid tissues has long engaged the attention of hematologists. As reviews of the principal theories have recently been given by Fineman [36] and by Downey,[37] the subject will not be discussed in detail. Suffice it to state that, in their reactions to the peroxydase solution, the primitive elements ("myeloblasts" and "lymphoblasts" of Naegeli) cannot be distinguished one from the other. Nor has it been possible, in the control preparations, to discern morphologic criteria by which they can be distinguished. It seems, therefore, that these cells are alike morphologically, and biologically as far as is indicated by their similar (negative) peroxydase reaction and their potential capacity for differentiation into either myeloid or lymphoid cells. The ferments are attributes acquired only in the process of differentiation along certain lines.

It appears inadvisable to denote this blood stem cell by either of the terms "myeloblast" or "lymphoblast," as they imply specificity that has not been proved to exist. In the counts that have been recorded, this cell is denoted by the term "hemocytoblast."

As the hemocytoblasts in both myelogenous and lymphatic leukemia contain no peroxydases, the diagnosis in cases in which they predominate cannot be made from the peroxydase reaction. However, it may usually (but not always) be made by careful morphologic study to determine the direction of differentiation of the hemocytoblast. Thus, in the case of acute myelogenous leukemia (Table 3) containing 75 per cent. hemocytoblasts, the diagnosis was made by the distribution of the other 25 per cent. As the latter included all stages of myeloid differentiation (myeloblasts, promyelocytes, myelocytes, metamyelocytes to polymorphonuclears), the diagnosis of myeloid leukemia was made (confirmed at necropsy); had it included stages in the transition from hemocytoblasts to lymphocytes, with absence of myeloid differentiation, the diagnosis of lymphatic leukemia would have been made. Undoubtedly, cases occur in which blood studies alone are insufficient for diagnosis, though these are exceptional. The frequent presence of myelocytes in lymphatic leukemia seldom causes difficulty, as all transition stages are not usually present.

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36. Fineman, S.: A Study of Microlymphoidocytic Leukemia, with the Report of a Case, Arch. Int. Med. **29**:168 (Feb.) 1922.

37. Downey, Hal: The Occurrence and Significance of the "Myeloblast" Under Normal and Pathologic Conditions, Preliminary Account, Arch. Int. Med. **33**:301 (March) 1924.

In those cases of hemocytoblastic leukemia[38] in which the hemocytoblasts fail to differentiate in either direction, the differential diagnosis of the tissue involved is not made from the blood. The leukemic cells, in these cases, are the mother cells of both myeloid and lymphoid tissues, and may arise in either.

SUMMARY

1. Leukocytic peroxydases demonstrable in blood smears by the benzidin method herein described occur only in those leukocytes which contain granules of one of the following types: (*a*) neutrophilic; (*b*) eosinophilic; (*c*) azurophilic granules of monocytes, and (*d*) azurophilic granules of the myeloblasts of Ferrata (promyelocytes of Naegeli), including Auer bodies.

2. Leukocytes totally devoid of granules do not react for peroxydases.

3. Elements containing the following types of granules do not react: (*a*) basophilic; (*b*) basophilic (immature) granules of eosinophil myelocytes; (*c*) azure granules of lymphocytes, and (*d*) granules of platelets and megakaryocytes.

4. The peroxydase reaction is of no value in differentiating hemocytoblasts in cases of myeloid leukemia from those of lymphoid leukemia.

5. The azurophilic granules of myeloid cells (myeloblasts of Ferrata) probably represent an early stage of myeloid transformation of the hemocytoblast.

6. The peroxydase reaction is of less value in diagnosis than the study of stained smears.[39]

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38. Ferrata, A.: Le Emopatie, Milan, **2**, 1923.

39. Since this paper was submitted for publication, Piney (J. Path. & Bacteriol. **28**:97 [Jan.] 1925) has reported observations on the oxydase reaction in three cases of acute myelogenous leukemia. Using the indophenol reaction controlled by a modified Kardos staining solution, Piney found that "a completely nongranular precursor of the granular leukocytes exists but does not give a positive oxydase reaction, which appears only in those cells in which granules are visible with suitable staining and illumination." The nongranular cells to which Piney refers as "myeloblasts" correspond to the hemocytoblasts in the terminology used in this paper. As shown above, they also react negatively for peroxydases.

BLOOD VOLUME

VI. THE RELATIONSHIP BETWEEN BLOOD VOLUME, TOTAL CORPUSCLE CONTENT AND ALKALINE RESERVE IN CASES OF PERNICIOUS ANEMIA *

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The work reported here was done in 1919. In view of the then prevailing association of a much reduced blood volume with pernicious anemia and the reported decrease in alkalinity of the serum, it seemed within the bounds of probability that if the total carbon dioxid elimination had to be taken care of by a reduced amount of blood, the level of the carbon dioxid in each unit of blood would be raised, and that the increase in hydrogen concentration resulting might in turn tend to maintain a reduced blood volume.

I therefore attempted to see to what such an hypothesis would lead by a study of the effect on blood volume of a decrease in the hydrogen ion concentration of the blood brought about by administration of carbonates to two patients with pernicious anemia who had received transfusions of unlike group blood. Changes in the concentration of the unagglutinable corpuscles were used as an index of change in volume of the blood.

The protocol of one of these cases, Case 59, has been given in detail elsewhere,[1] and will simply be reviewed here. An obese woman with an extremely low blood volume, as indicated by the count of unagglutinable corpuscles, began to take bicarbonate. Two days later, the blood volume was apparently greatly increased; seven days later, the count of the unagglutinable corpuscles indicated the normal blood volume proportion of 82 c.c. for each kilogram of body weight, which remained constant, but as at this time the transfused blood had been in the patient's circulation for thirty-three days, it was questionable whether this drop in the unagglutinable corpuscles indicated a dilution due to increase in blood volume, or one of these intermittent periods of elimination by which the transfused blood is removed from the circulation, which happened to be coincident with the initiation of the administration of the bicarbonate.

In a second case, Case 61 (Table 1), after three transfusions the patient began to take sodium bicarbonate, beginning with the small dose of 0.67 gm. a day, and gradually increasing the dose. The apparent blood volume, as indicated by the transfused corpuscles derived from the

* From the Mayo Foundation.

1. Ashby, Winifred: Study of Blood Volume, V, The Effect of Treatment on the Blood Volume of Patients with Pernicious Anemia, Arch. Int. Med. **35**: 733 (June) 1925.

unlike group transfusion given seventeen days before, was 66 c.c. for each kilogram of body weight one day after administration of the bicarbonate was instituted. An apparent gradual increase in blood volume followed, until, ten days later, the decrease in the count of unagglutinable corpuscles indicated a dilution such that the volume was 111 c.c. for each kilogram of body weight. At this time, a fresh transfusion of unlike group blood was given. The data derived from it indicated a blood volume of 109 c.c. for each kilogram of body weight. This close approximation between the volume obtained on the injection of fresh unagglutinable corpuscles and that indicated by the count of the transfused corpuscles that had been in the circulation for twenty-

TABLE 1.—*Findings in Case 61*

A man, aged 42, with pernicious anemia, who was very weak, received his first series of transfusions, which did not greatly improve his condition. He died shortly after his return home.

Days of Treatment	Red Cell Count in Millions	Corpuscles for Each Kilogram of Body Weight	C.c. of Blood for Each Kilogram of Body Weight	Remarks
	Transfusion of unlike group blood			
0	1.70	95×10^9	56	Throbbing sensations
1	1.77	106×10^9	60	Throbbing sensations
3	1.88	117×10^9	62	Throbbing sensations
6	1.57	102×10^9	65	Throbbing ceased
9	Transfusion			
14	2.03	107×10^9	51	
14	Transfusion			
15	2.25	115×10^9	51	
16	Patient began taking sodium bicarbonate, 0.67 gm. a day			
17	2.16	143×10^9	66	
19	1.94	134×10^9	69	Patient said that he felt better and had an appetite for the first time
20	2.30	150×10^9	69	
24	2.05	152×10^9	74	Patient felt better
27	1.56	173×10^9	111	
	Transfusion of unlike group blood			
27	2.12	231×10^9	109	
28	2.57	194×10^9	74	Patient had discontinued bicarbonate while in hospital for transfusion
29	2.76	284×10^9	103	Patient had taken 4 gm. of bicarbonate; urine acid
30	2.33	254×10^9	109	
31	2.57	257×10^9	100	Patient had taken 7.33 gm. bicarbonate; urine acid

seven days would reduce the probability that the apparent increase in blood volume had been due to elimination of the transfused corpuscles rather than to dilution from an increased blood volume. However, it is not absolute evidence.[2] While the patient was in the hospital for this transfusion, he took no sodium bicarbonate. The following day, the concentration of the unagglutinable corpuscles was such as to indicate a decrease in blood volume to 74 c.c. for each kilogram of body weight.

2. Ashby, Winifred: Study of Blood Volume, III, Apparent Changes in Blood Volume Indicated by Transfusion, and Their Bearing on Methods of Determining Blood Volume by Means of the Degree of Change in a Constituent of the Blood, Following Transfusion of a Known Amount of That Constituent, Arch. Int. Med. **35**:641 (May) 1925.

Administration of bicarbonate was resumed, in larger amounts, and after a day a blood volume of 103 c.c. for each kilogram of body weight was indicated by the count of the transfused unlike group blood corpuscles. This was maintained for the next two days, while the patient was under observation, during which bicarbonate was taken.

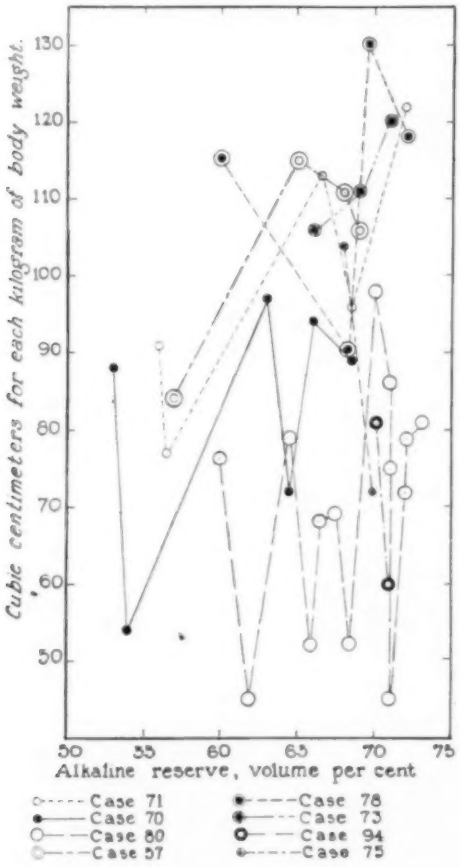

Fig. 1.—Alkaline reserve in eight cases of pernicious anemia, plotted against simultaneous blood volumes calculated in terms of cubic centimeters for each kilogram of body weight.

As these results seemed to indicate a relationship between blood volume and alkalinity, an attempt was made to correlate the alkaline reserve with the apparent blood volume as indicated by the concentration of the unagglutinable corpuscles following a transfusion of unlike group

TABLE 2.—*Correlation of the Total Red Cell Count, the Blood Volume and the Alkaline Reserve in Patients with Pernicious Anemia*

Case	Days	Red Cell Count in Millions	Corpuscles for Each Kilogram of Body Weight	C.c. of Blood for Each Kilogram of Body Weight	Alkaline Reserve, per Cent. by Volume	Time
71	Transfusion, 500 c.c.					
	0	0.88	57 × 10⁹	73	..	
	1	1.00	.....	..	57	
	2	1.06	.....	..	51	
	3	1.07	84 × 10⁹	..	..	
	4 Transfusion, 500 c.c.					
	5	1.62	123 × 10⁹	..	56.5	
	8	1.23	112 × 10⁹	91	56	
	14	1.09	133 × 10⁹	122	72	
	14 Transfusion, 500 c.c.					
	16	1.38	138 × 10⁹	100	..	
	18	....	.....	113	66.5	
	18 Transfusion, 500 c.c.					
	18	1.53	147 × 10⁹	96	68.5	
70	Transfusion, 500 c.c.					
	0	1.02	55 × 10⁹	54	54	
	1	1.28	96 × 10⁹	72	64.5	Morning
	1	....	.....	..	60	Evening
	2	1.17	.....	..	57	
	4	0.88	77 × 10⁹	88	53	
	4 Transfusion, 500 c.c.					
	5	1.11	108 × 10⁹	97	63	
	8	1.40	131 × 10⁹	94	66	
	11 Transfusion, 500 c.c.					
	14	1.79	159 × 10⁹	89	68.5	
80	0	1.17	.....	..	71.5	
	Transfusion, 500 c.c.					
	0	1.26	59 × 10⁹	47	71	p.m.
	3	....	.....	47	62	5:30 p.m.
	4	....	.....	72	72	9:30 a.m.
	4	2.25	117 × 10⁹	52	66	8:30 p.m.
	5	1.76	134 × 10⁹	76	60	9:00 p.m.
	6	1.93	189 × 10⁹	98	70.5	9:00 a.m.
	6	1.96	133 × 10⁹	68	66.5	8:30 p.m.
	7	1.93	153 × 10⁹	79	72	10:00 a.m.
	7	1.99	150 × 10⁹	75	71.5	3:00 p.m.
	7	2.06	146 × 10⁹	69	67.5	6:00 p.m.
	10	2.21	180 × 10⁹	81	73	9:00 a.m.
	10 Transfusion					
	11	1.51	119 × 10⁹	79	64.8	9:00 a.m.
	16	2.06	107 × 10⁹	52	68.5	9:00 a.m.
	17	....	.....	86	..	
57	0	1.16	.....	..	57	
	0 Transfusion (second in series)					
	0	1.48	161 × 10⁹	111	68	
	7	1.30	150 × 10⁹	115	65	
	7 Transfusion					
	7	....	.....	..	60	
	9	1.72	183 × 10⁹	106	69	
	10	1.23	105 × 10⁹	84	57	
78	0	0.71	.....	..	70	
	0 Transfusion					
	0	..	.....	...	67	
	1	0.96	114 × 10⁹	119	..	
	4	1.12	101 × 10⁹	90	68	
	19	1.54	200 × 10⁹	130	69.5	10:00 a.m.
	19	1.42	163 × 10⁹	115	60	9:00 p.m.
	20	1.27	150 × 10⁹	118	72	
73	0	1.33	.....	...	67	
	0 Transfusion					
	0	1.32	222 × 10⁹	145	..	
	6	1.60	193 × 10⁹	120	71	
	9	1.94	204 × 10⁹	106	66	
	10	2.09	.....	...	60.5	a.m.
					60.5	p.m.
	13	2.13	250 × 10⁹	111	69.5	a.m.
	13 Transfusion					
	13	....	.....	..	57	p.m.
	20	....	.....	..	64	
	21	3.22	.....	..	..	
	22	....	.....	..	65	p.m.
	23	2.32	.....	..	66	a.m.
	30	2.62	.....	..	63	
	36	2.21	.....	..	72.5	p.m.
	37	2.51	.....	..	58	a.m.

TABLE 2.—*Correlation of the Total Red Cell Count, the Blood Volume and the Alkaline Reserve in Patients with Pernicious Anemia—Continued*

Case	Days	Red Cell Count in Millions	Corpuscles for Each Kilogram of Body Weight	C.c. of Blood for Each Kilogram of Body Weight	Alkaline Reserve, per Cent. by Volume	Time
94	0 Transfusion (third in series)					
	11	2.50	150 × 10⁶	60	71	a.m.
	11	....	.....	..	73	p.m.
	14	3.03	243 × 10⁶	81	70	
75	0	1.90	.....	..	66	
	0 Transfusion					
	0	2.22	160 × 10⁶	72	70	
	3	....	.....	..	65	
	3 Transfusion					
	3	2.48	256 × 10⁶	104	66	
60	.....	2.01	.....	..	59	
					57	
		Patients with Secondary Anemia				
76	0	...	.....	...	62	
	0	....	.....	...	63	
	16	....	.....	...	62	
86	0	3.66	378 × 10⁶	104	74.5	p.m.
	1	3.58	308 × 10⁶	87	64.5	a.m.
	2	3.22	300 × 10⁶	98	75.5	p.m.

blood. The alkaline reserve was determined from the urine by the method of Van Slyke and Fitz [3] (Table 2). The blood volumes, as determined by the count of unagglutinable corpuscles derived from the unlike group transfusion given at the beginning of each study, have not been included beyond the point at which it seemed improbable that there had been any elimination of transfused blood. All the alkaline reserve determinations are included.

Although the first two studies appeared to show a rather marked parallelism between alkaline reserve and blood volume percentage, this relationship did not hold with the study of further cases. I therefore concluded that there was no relationship between the two, and that the apparent increases in volume following administration of carbonates in Cases 59 and 61 were a matter of accident. On further analysis, however, there seems to be a slight tendency for alkaline reserve to increase when the apparent blood volume increases, but a tendency for parallelism becomes much greater when the blood volume for each kilogram of body weight is multiplied by the red cell count. In Figures 1 and 2, alkaline reserve is plotted against the blood volume for each kilogram of body weight in one instance, and the number of corpuscles for each kilogram of body weight in the other. The points that indicate the readings for individual patients are connected, but the general trend of the curves would seem to be more significant than the individual curves.

3. Fitz, R., and Van Slyke, D. D.: Studies of Acidosis, IV, The Relationship Between Alkaline Reserve and Acid Excretion, J. Biol. Chem. **30**:389-400 (June) 1917.

SUMMARY AND CONCLUSION

In patients with pernicious anemia, the alkaline reserve, as determined by the method of Van Slyke and Fitz, was frequently found to fall below the normal limits (from 63.1 to 77.5) given by those authors, but after transfusions it tended to be normal.

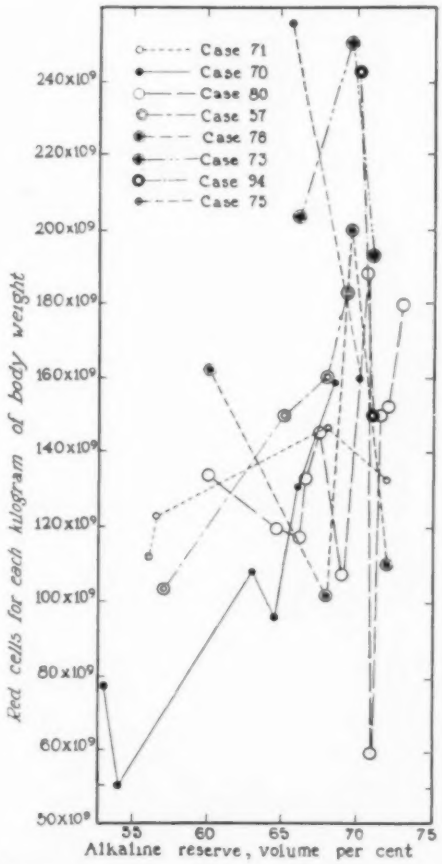

Fig. 2.—Alkaline reserve in eight cases of pernicious anemia, plotted against total number of corpuscles present for each kilogram of body weight.

Although there is a great deal of variation, possibly due to variation in the amount of strain put on the carbon dioxid eliminating mechanism by exercise and so forth, it would appear from these data that there is a slight tendency for the alkaline reserve to increase with the blood volume, but that there is a greater tendency for the alkaline reserve to

increase with the increase in the total number of corpuscles present for each unit of body weight. In view of the fact that Henderson, Bock, Field and Stoddard [4] consider that hemoglobin is responsible for the transfer of 90 per cent. of the carbon dioxid from the tissues to the lung, this is not surprising.

The much more marked relationship between the hemoglobin content and the alkaline reserve than between the blood volume and the alkaline reserve would suggest that the increased alkaline reserve may merely be the effect of the increased carbon dioxid carrying capacity of the blood, and may not have any causal effect on increase in blood volume.

4. Henderson, L. J.; Bock, A. V.; Field, H. Jr., and Stoddard, J. L.: Blood as a Physicochemical System, II, J. Biol. Chem. **59**:379-431 (March) 1924.

ACUTE INTESTINAL OBSTRUCTION

III. SIMPLE OBSTRUCTION *

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During the last two decades, a vast amount of interesting work has been done on acute intestinal obstruction in an endeavor to find the lethal factors involved. Beyond keeping the subject alive in the experimental field, much of the work has added little to the ultimate settlement of the questions at issue. Complicated operative procedures, ether and morphin anesthesia, methods used because of preconceived premises of toxic substances, and the failure to recognize different types of obstruction have been the main stumbling blocks.

In the preceding papers,[1] we have demonstrated that experimental obstruction produced under local anesthesia gives most ideal results. The postoperative animals are in practically the same condition as the human patients seen clinically. The only complicating factors in the experimental work are the procain anesthesia and the 3 inch (7.6 cm.) incision through the linea alba.

Carefully checked control animals on which only the abdominal incision has been made show that these two factors cause little or no systemic reaction.

Obstruction thus produced demonstrates clearly that there are two types of acute intestinal occlusion: (1) Acute strangulation. This includes those cases in which there is an interference with the venous, arterial and lymphatic circulation in the bowel wall and mesentery as well as complete obstruction of the intestinal lumen. Under this heading are grouped volvulus, strangulated hernia and intussusception. This condition is characterized by rapid pulse and respiration, subnormal temperature and low blood pressure, as well as the usual obstruction symptoms. Death here is due to shock, toxemia and peritonitis. (2) Acute simple obstruction. This comprises those cases in which there is a complete blockage of the bowel lumen only, with practically no circulatory involvements. Here the obstruction is produced by gall-

* From the Departments of Anatomy and Physiology, University of Oregon Medical School.

1. Hausler, R. W., and Foster, W. C.: Studies of Acute Intestinal Obstruction, I, Different Types of Obstruction Produced Under Local Anesthesia, Arch. Int. Med. **34**:97 (July) 1924; II, Acute Strangulation, ibid. **34**:697 (Nov.) 1924.

stones, enteroliths, foreign bodies, adhesions and bands. The temperature, pulse, respiration and blood pressure show no marked deviation from the normal, even after ten days, although the obstruction symptoms are very pronounced.

Acute strangulation has been dealt with in a previous paper. In this paper, we shall endeavor to show that death in simple intestinal obstruction is not due to a toxemia, as is generally assumed, but instead is due to starvation.

In experimental simple obstruction, occlusion of the bowel lumen is usually produced by clamps, ties or section of the intestine and inversion of the cut ends. All three of these methods have their disadvantages and introduce certain complications which must be considered when interpreting the results obtained. The ideal method of producing obstruction is naturally that seen in human cases, namely by bands of living tissue. The aluminum clamps, as first used by Hartwell and Hoguet,[2] are not very satisfactory because of the difficulty in determining definitely whether the obstruction has been complete. Tissue destruction, abscess formation and peritonitis are rather frequent complications. Ligation of the intestine, with silk or cord ties, produces good results for several days, but unfortunately the ligature cuts through the intestinal wall in four or five days, and the bowel reunites or death follows from perforation and peritonitis. Section of the intestine and inversion of the proximal and distal stumps gives a complete obstruction that is easily produced and very permanent. This technic, however, causes considerable tissue destruction and is followed by a severe constitutional reaction. The postoperative record shows that for the first five or six days, or until the inverted stumps have healed, there is a quite pronounced rise in temperature, pulse and respiration. Unless subcutaneous injections of fluid are given during this reparative period, many of the animals die. However, if the dogs survive, we have an ideal obstruction exactly comparable to that seen in human cases. The obstruction is complete, and little or no devitalized tissue is present. The writers have used all three methods and find that the section method gives the most satisfactory results.

LITERATURE

No attempt will be made to review the extensive literature on the subject of intestinal obstruction. Instead, the reader is referred to a recent article by Ellis.

The literature shows five main theories as to the cause of death in acute intestinal obstruction:

1. Bacteremia. The theory that death is due to a bacteremia at first sight seems very plausible. McClure [3] has shown that the fluid accumu-

2. Hartwell, J. A., and Houget, J. P.: An Experimental Study of High Intestinal Obstruction, Am. J. Med. Sc. **143**:357, 1912.

3. McClure, R. D.: An Experimental Study of Intestinal Obstruction, J. A. M. A **49**:1003 (Sept. 21) 1907.

lating in the intestines above the obstruction acts as a very good culture medium. It furnishes all the requirements for bacterial growth, i. e., food, water, proper temperature and an alkaline reaction. Furthermore, the normal intestinal tract is the habitat of innumerable pathogenic bacteria. Under such ideal conditions, they multiply very rapidly and thus might easily work their way through the intestinal mucosa into the blood stream.

However, Krafft,[4] McClure,[3] and Hartwell and Hoguet [2] have definitely disproved this theory by showing that at death the heart's blood, peritoneum and organs are practically always sterile.

2. Perverted secretion. Supporters of this theory state that, after obstruction, the intestinal mucosa of the proximal segment secretes a toxin which when absorbed is rapidly fatal.

Dragstedt, Moorhead and Burcky [5] showed the fallacy of this theory by draining open isolated duodenal and jejunal loops into the peritoneal cavity. Their dogs lived indefinitely and showed no toxic symptoms.

3. Shock theory. The clinical evidence of tachycardia, low blood pressure and profound collapse, combined with wide dilatation of all splanchnic vessels, point to severe disturbance of the cardiovascular system.

These symptoms are true indications of shock and, as previously stated, appear in practically all cases of acute strangulation.

The protocols of dogs with simple intestinal obstruction, produced under local anesthesia, show an almost complete absence of shock symptoms. The pulse and respiratory rates are always practically normal; the temperature curve shows only the usual diurnal variation, and the blood pressure remains the same even after twenty days.

Shock, however, is an acute affair always manifesting its symptoms within the first twenty-four hours. These simple obstruction dogs live three or four weeks. It is thus evident that shock is not a lethal factor in simple intestinal obstruction.

4. Toxemia. This theory states that death in acute intestinal obstruction is due to the absorption of poisons produced by bacterial action on the stagnant bowel fluids which accumulate in the intestine above the obstruction. This theory, which has received almost universal

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4. Krafft, quoted from Enderlain, Hotz: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:755, 1911.

5. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: Experimental Study of Intoxication in Closed Intestinal Loops, J. Exper. Med. **25**:421 (March) 1917.

acceptance, has been supported by experiments demonstrating that death is quickly produced when these fluids are injected intravenously into normal animals. Thus far, no one has been able to demonstrate toxins in the blood stream or their absorption by the intestinal mucosa.

5. Dehydration. In 1912, McLean and Andries [6] and Hartwell, Hoguet and Beekman,[2] each group working independently of the other, concluded that the water loss from drainage of the body fluids into the intestinal lumen above the obstruction was the cause of the systemic symptoms and the eventual cause of death.

This dehydration theory seems very plausible, since clinically we know that the mechanical obstruction causes an almost immediate vomiting of all foods and liquids taken, and, in addition, that the profuse vomitus contains a considerable quantity of bile, pancreatic, gastric and intestinal secretions.

The last two theories have never been definitely proved or disproved.

METHODS

The operative procedures used were substantially the same as those described in the preceding papers. All work was done on healthy dogs under aseptic technic. Blood chemistry estimations were made at frequent intervals by the methods previously reported. Blood pressure readings were made on the femoral artery under local anesthesia.

EXPERIMENTAL WORK

Rôle of Toxemia.—In our previous work on acute intestinal strangulation, it was noted that even massive doses of ten hour strangulated loop fluid was relatively nontoxic when injected intraperitoneally into normal dogs. This bloody exudate is an ideal culture media, even more so than intestinal secretions.

It thus seemed probable that the vomitus of simple obstruction was likewise nontoxic, especially since dogs of the simple obstruction group vomit at least three or four times a day, and thus prevent prolonged bacterial action on the accumulating fluid. Most high obstruction vomitus is not exposed to bacterial action for more than a twelve hour period. Selective action of the intestinal mucosa and vomiting also prevent much toxin absorption.

To determine, therefore, the relative toxicity of high obstruction vomitus, the total daily vomitus of four dogs with simple duodenal cord tie obstruction was collected, centrifugated, filtered through ordinary filter paper and slowly injected subcutaneously into normal dogs of approximately the same size. All vomitus was prepared, and injected as

6. McLean, A., and Andries, R. C.: Ileus Considered Experimentally, J. A. M. A. **59**:1614 (Nov. 2) 1912.

soon as possible after it was obtained in order to prevent further bacterial action. The vomitus was not heated because of the objection that this might destroy the toxins as well as the bacteria. However, by this technic we were injecting millions of bacteria into the subcutaneous tissue of these dogs. Apparently, dogs have good resistance to bacteria since only one of these dogs developed skin abscesses following the three days' injection period.

Table 1 shows the most severe reaction noted.

Two days later, the dog had recovered entirely.

The experiments in Table 1 show practically no toxic effect from the absorption of this high obstruction vomitus, and we therefore conclude

TABLE 1.—*Data Proving That High Duodenal Obstruction Fluid Is Relatively Nontoxic*

Dog 1, a male, weight 16 pounds (7.3 kg.). Prepared vomitus injected subcutaneously.

Day	Time	Vomitus	Result
1	9 a. m.	60 c. c.	Vomitus appeared to have no effect on dog
	12	60 c.c.	
	1 p. m.	60 c.c.	
	3	60 c.c.	
	5	60 c.c.	
2	9 a. m.	50 c.c.	Temperature, 103.2
	12	65 c.c.	Dog slightly indisposed
	1 p. m.	60 c.c.	
	3	60 c.c.	
	5	60 c.c.	
3	9 a. m.	65 c.c.	Temperature, 103
	12	60 c.c.	Dog looked sick; evidently had bacteremia from injections
	1 p. m.	50 c.c.	
	3	50 c.c.	
	5	50 c.c.	

that even the total daily vomitus is relatively nontoxic when injected subcutaneously, as soon as possible after it is obtained. Since we know that the fluid current is mainly out of the body by way of the upper intestinal tract and is very large, it is evident that only slight absorption of toxins can occur.

Death from toxemia thus seems very improbable. What then is the cause of death? Perverted secretion and bacteremia have been disproved. Shock, we have shown, is not present. Starvation and dehydration appear to be the only remaining possibilities.

Rôle of Dehydration.—Most workers assert that, since death is early and vomiting almost negligible, dehydration cannot be a prominent lethal factor. Their operations were invariably under ether anesthesia, and the animals usually died in from three to five days. No fluids were given subcutaneously, and little vomiting was noted.

On the other hand, in the experimental work of Hartwell and Hoguet,[2] Bacon and Anslow and Eppler,[7] reports are made of the

7. Bacon, D. K.; Anslow, R. E., and Eppler, H. H.: Intestinal Obstruction, Arch. Surg. **3**:641 (Nov.) 1921.

marked daily fluid output and loss of body weight in dogs of the simple obstruction type. They, however, had given daily subcutaneous injections of large quantities of saline solution and, under these conditions, the vomitus and urinary excretions were naturally much larger than they would have been had they allowed the body fluids to be gradually depleted, as they are in the ordinary cases.

With this fluid loss in mind, the clinical literature was examined for reports of total fluid output in human cases of obstruction, but none were found.

TABLE 2.—*Fluid Loss in Low Duodenal Obstruction*

Dog	Weight	Days	Urine and Vomitus	Result
1	18.5 pounds (8.4 kg.)	1	180 c.c.	Dead in 60 hours from perforation and peritonitis
		2	520 c.c.	
	15.4 pounds (7 kg.)	3	100 c.c.	
2	43 pounds (19.5 kg.)	1	610 c.c.	Recovered after 90 hours
		2	415 c.c.	
		3	180 c.c.	
	37.1 pounds (16.8 kg.)	4	95 c.c.	
3	24 pounds (10.9 kg.)	1	285 c.c.	Died after 68 hours from perforation
		2	335 c.c.	
	19.2 pounds (8.6 kg.)	3	950 c.c.	
4	20 pounds (9 kg.)	1	375 c.c.	Recovered on third day
	19.1 pounds (8.6 kg.)	2	275 c.c.	
		3	195 c.c.	
	17.2 pounds (7.8 kg.)			
5	11 pounds (5 kg.)	1	100 c.c.	Recovered on third day
	10.1 pounds (4.5 kg.)	2	115 c.c.	
	9.5 pounds (4.3 kg.)	3	80 c.c.	
6	20.4 pounds (9.2 kg.)	1	210 c.c.	Recovered on fifth day
	19.9 pounds (9 kg.)	2	180 c.c.	
	19.3 pounds (8.7 kg.)	3	240 c.c.	
	18.9 pounds (8.6 kg.)	4	130 c.c.	
	18.1 pounds (8.2 kg.)	5	65 c.c.	
7	30.5 pounds (13.8 kg.)	1	250 c.c.	Recovered on fourth day
	29 pounds (13.2 kg.)	2	185 c.c.	
	28.3 pounds (12.8 kg.)	3	195 c.c.	
	27.8 pounds (12.6 kg.)	4	105 c.c.	

We therefore experimented on a series of seven dogs with simple duodenal and ileal obstruction; an accurate record was kept of daily fluid loss by urine and vomitus. Operations were performed, under local anesthesia, to prevent the usual atonic postoperative conditions of the bowel. The dogs were kept in metabolism cages so constructed that all fluid excretions could easily be collected. The obstruction was produced by ligating the bowel with a heavy cord tied just tight enough completely to block the bowel lumen. These ties cut through the bowel wall at the end of four or five days, and the vomiting immediately ceased, thus indicating that the obstruction had been relieved.

These results, although observed over only a short period of time, show that fluid loss is quite pronounced.

In another series of six dogs in which obstruction was produced by section of the intestine and stump inversion, this daily fluid loss was replaced by subcutaneous injections of physiologic sodium chlorid solution. The results were as follows: One dog died of snuffles on the fifth day; another was killed on the twelfth day because of a large skin abscess, and the remaining four lived fourteen, sixteen and seventeen days, respectively.

Table 3 shows the usual temperature, pulse and respiratory variations noted.

The foregoing results confirmed the work of Hartwell and Hoguet,[8] who first showed that, in simple intestinal obstruction, if the fluid loss

TABLE 3.—*Typical Temperature, Pulse and Respiration in Obstruction of Lower Jejunum*

Dog 2, weight 55 pounds (24.9 kg.), a large, black male.

Days Before	Rectal Temperature	Pulse	Respiration	Blood Pressure	Sodium Chlorid, C.c.	Result
1	101.4	84	18	150		
1	99.2	86	20		250	
2	101.0	126	18		250	
3	102.2	102	22		300	
4	102	88	20		300	
5	102.8	84	18		300	Slight nasal discharge
6	102.4	88	20		300	
7	102	76	18		350	
8	101.9	90	10		250	
9	101.1	66	18		350	
10	100.4	58	16		400	Snuffles worse
11	100.4	56	16		350	
12	100.4	54	20		400	Snuffles better
13	101	58	22		350	
14	100.6	74	18		300	
15	101	92	20		340	
16	100.4	172	20	100 systolic	300	
17		Died				Weight 41 lbs. (18.6 kg.)

Necropsy: Obstructed viscera grossly normal; no peritonitis; proximal and distal stumps well healed; lower 6 inches (15.2 cm.) of proximal intestine dilated slightly, and walls hypertrophied.

is replaced, the animals will live two or three weeks. They also indicated that fluid loss is a very important lethal factor in simple intestinal obstruction. That dehydration, however, is the sole cause of death seems very improbable. It certainly does not explain the rapid death obtained in experimentally produced obstruction. Fluid loss through vomitus and excretions is never sufficiently pronounced in obstruction to cause death in one, five or even ten days. All high obstruction dogs died in less than a week unless given fluid subcutaneously. It seemed apparent, therefore, that in experimental work there must be some complicating factor due to the operative procedure.

A careful review of the literature showed that, of the three methods used in producing obstruction, only one gave satisfactory results. Cord

8. Hartwell, J. A.; Hoguet, J. P., and Beekman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701-736, 1914.

tie and clamp occlusion were too uncertain and too temporary, and perforation and peritonitis were very common. With section of the intestine and inversion, the obstruction was very satisfactory, but the animals died in about five days unless given fluids subcutaneously. It appeared evident, therefore, that in the latter method the time during which healing of the inverted raw ends was taking place was a critical period. The animals that survived this stage should give ideal experimental results.

Consequently, on a series of four dogs, cut and inversion obstruction was produced, and physiologic sodium chlorid solution was given subcutaneously, during the first five days, to tide them over this reparative

TABLE 4.—*Simple Obstruction of Lower Duodenum*

Dog 4, an adult, female collie, weight 34.2 pounds (11 kg.).

Days	Temperature	Pulse	Respiration	Vomitus, C.c.	Saline Solution, C.c.	Chlorids, Mg. per 100 C.c.	Carbon Dioxid	Nitrogen, Mg. per 100 C.c.	Blood Pressure	Observation
0	102.2	110	18	...	...	298	43.2	23	not taken	
1	103.2	152	24	...	250	...	.....	..	...	
2	102.9	144	24	...	250	...	.....	..	...	
3	102.6	148	22	...	240	...	.....	..	...	
4	103.1	145	24	...	240	...	.....	..	...	
5	104	140	22	...	250	...	.....	..	...	Urine scanty during remainder of starvation period
6	103.6	135	22	...	...	...	.....	..	...	
7	103.5	140	20	...	...	...	.....	..	...	
8	103	138	20	...	...	...	.....	..	...	
9	103.1	135	20	...	...	...	.....	..	...	
10	102.7	128	16	...	...	...	.....	..	...	
11	103.4	128	18	...	...	320	46.2	..	138 systolic	
12	102.6	160	12	...	...	...	.....	..	...	
13	102.6	164	18	...	...	298	60.49	..	...	
14	102.7	176	16	...	...	...	.....	..	...	
15	102.6	176	12	...	...	...	.....	..	...	Mucosa of nasal and buccal cavity dry and crusted
16	102.1	172	9	...	...	...	.....	..	...	
17	142.1	172	11	...	...	310	53.6	40	...	
18	101.8	176	10	...	...	...	.....	..	...	
19	102.7	160	10	150	...	320	35.8	54	...	
20	103.6	165	12	...	...	...	.....	..	105	
21	102.1	Killed in afternoon				330	42.5	67	...	

Necropsy (done immediately): Weight 19.3 pounds (8.7 kg.). Abdominal viscera grossly normal; no peritonitis; stumps well healed; walnut sized abscess in mesentery just below proximal intestine. Weights of viscera, as follows: Liver, 272 gm.; kidneys, 76 gm.; spleen, 10.5 gm.; thyroid, 4 gm.; suprarenals, 3.2 gm.; pancreas, 21 gm., and ovaries, 1.4 gm.

period. Complete food and water starvation was then begun. One animal died on the third day from hemorrhage in the proximal segment; another developed snuffles and was sacrificed on the fifth day. The remaining two dogs, to our amazement, lived twenty-one and twenty-eight days, respectively. In other words, these animals lived sixteen and twenty-three days without food, water or salts, with complete obstruction of the small intestine. Tables 4 and 5 show the postoperative results.

These two animals, especially during the last ten days, showed the typical picture of starvation. The loss of weight was extreme. The skin became dry and inelastic, and the shedding of hair was pronounced.

Folds produced in the skin flattened very slowly. Salivary secretion ceased entirely, and as a result the tongue and oral mucosa became crusted with foul smelling, dry serous placques. The last five days, the nasal apertures became plugged with similar secretions and nasal breathing was harsh and difficult. The skin was extremely anesthetic, so much so that incisions caused no pain. The extremities were cold and the blood flow through them of such small volume that the necessary amount of blood for chemistry estimations was difficult to obtain. The rectal

TABLE 5.—*Simple Obstruction of Upper Jejunum*

Dog 5, an adult, female mongrel, weight, 51 pounds (23.1 kg.).

Days	Temperature	Pulse	Respiration	Vomitus, C.c.	Saline Solution, C.c.	Chlorids, Mg. per 100 C.c.	Carbon Dioxid	Nitrogen, Mg. per 100 C.c.	Blood Pressure	Remarks
0	101.9	90	18	...	...	315	45.2	23	not taken	
1	103.2	148	18	...	370	...	....	..	...	Condition good
2	102.6	140	22	...	240	...	....	..	...	Condition good
3	102.1	136	20	...	240	...	....	..	...	Condition good
4	101.8	66	18	...	240	...	....	..	...	Condition good
5	102.9	64	18	...	250	...	....	..	...	Condition good
6	102.2	68	18	...	none	...	....	..	...	Condition good
7	102.3	64	18	...	...	...	....	..	...	Urine scanty
8	101.8	72	16	...	...	...	....	..	...	
9	102.2	68	18	300	...	...	....	..	..	
10	102	88	22	...	...	...	....	..	...	
11	103.3	96	20	130	...	310	60.4	40	143	
12	102.6	98	12	...	...	...	....	..	...	
13	102.4	126	20	250	...	300	66.5	38.2	...	
14	102.6	143	20	...	...	...	....	..	...	
15	101.5	160	18	15	...	...	....	..	...	
16	102.4	156	16	300	...	...	....	..	...	
17	102.1	138	16	180	...	300	56.4	46	...	Nose dry; respiration harsh; crusts on nose and lips
18	101.6	134	17	...	...	...	....	..	...	
19	101.6	114	16	...	...	...	....	..	...	
20	100.4	124	12	...	...	...	....	..	...	
21	100.1	146	14	...	...	270	53.7	45	...	
22	101	150	14	...	...	...	....	..	...	
23	101.2	140	12	...	...	...	....	..	...	
24	102.2	160	14	50	...	290	57	41.6	..	
25	101.8	132	15	...	...	...	....	..	...	
26	101.9	145	16	...	...	...	....	..	112	
27	101.8	160	16	410	...	280	62.7	42	...	
28	102.2	165	18	...	..	...	....	..	...	Sudden death

Necropsy (immediate): All thoracic and abdominal viscera grossly normal; no peritonitis; lower 3 inches (7.6 cm.) of proximal intestine slightly dilated and walls hypertrophied. Distal segment very small and atrophic. Weights of organs, as follows: Liver, 254 gm.; kidneys, 78 gm.; spleen, 12 gm.; thyroid, 3 gm.; suprarenals, 3 gm.; pancreas, 14 gm., and ovaries, 1.2 gm.

temperature was slightly subnormal; the pulse almost doubled in rate, and the respirations were very slow. The blood pressure fell to about 110 mm. of mercury systolic.

Throughout the experiment the dogs were active and playful and, except for thirst, vomiting and the symptoms mentioned, appeared absolutely normal. At no time after the first five days was there any subjective or objective evidence of toxemia. The temperature, pulse and respiratory changes were certainly not those of toxemia, and the appearance and action of the animals were essentially those of a normal animal undergoing starvation.

The red blood cell count was consistently above normal after the first week, the counts varying between six and eight million. Hemoglobin estimations (Haskins-Osgood modification of Sahli) fluctuated between 120 and 135 per cent. Viscosity determinations were made by comparing the time required (stop-watch) for normal oxalated blood to flow from a special 5 c.c. viscosity pipet with that for the oxalated blood of the obstruction animals. This method, although not absolutely accurate, gave approximate results and revealed a quite decided increase in blood viscosity. This increase was also visibly apparent, the blood appearing thick and flowing very slowly. Clotting time was decreased, and no bleeding occurred following small skin incision. A comparison of the foregoing charted blood chemistry figures with those of Dog 5 of Morgulis and Edwards'[9] starvation series (the only animal deprived of both food and water) shows that the changes are almost identical. The chlorids remain normal or slightly increase; the nonprotein nitrogen increases gradually although never to a very high figure, and the carbon dioxid combining power of the blood varies, usually slightly above normal limits. These changes are all indicative of the anhydremia of starvation.

A rather unique case of simple intestinal obstruction was seen by us several months ago and will be reported here, as it represents the type of obstruction produced by gallstones, foreign bodies and enteroliths. The owner of a large Airedale brought the animal to the medical school for treatment. He stated that the dog was poisoned about two weeks before, as a result of eating fresh salmon (common in Northwest). During this time, the dog had vomited all food and water eaten, had lost markedly in weight and strength, and when seen was in a precarious condition. Subcutaneous injections of physiologic sodium chlorid solution were given at once, but with little results, the dog dying on about the eighteenth day after the onset of the obstruction symptoms. At necropsy, a round basalt stone, about 2 inches (5 cm.) in diameter, was found tightly lodged in the lower ileum above 5 inches (12.7 cm.) above the ileocecal valve. The small intestine above this point was markedly dilated, congested and contained a small quantity of fluid. No perforation or peritonitis was present, and the obstruction was complete. This case further substantiates the belief that starvation is the cause of death in simple obstruction.

COMMENT

It has been previously demonstrated that in uncomplicated cases of acute simple intestinal obstruction, bacteremia and perverted secretion

9. Morgulis, S., and Edwards, A. C.: Chemical Changes in the Blood During Fasting and Subsequent Refeeding, Am. J. Physiol. **68**:477 (May) 1924.

of the intestinal mucosa are not the causes of death. Shock, the predominating lethal factor in acute strangulation of a large segment of intestine, is never present in simple obstruction. A review of the temperature, pulse and respiration and blood pressure curves of the accompanying tables shows a complete absence of shock symptoms. This theory, therefore, appears untenable.

That death is due to a toxemia is also very improbable for the following reasons:

1. The relatively slight toxicity of even large quantities of vomitus.

2. The decreased absorption from the proximal segment.

3. The fact that dogs with closed, isolated loops full of extremely toxic fluids live months without showing marked toxic manifestations.

4. The quicker death in high obstruction (in this the function of the intestine is mainly secretory), and the slower death in low obstruction, in which normally much absorption occurs, and in which the intestinal secretions become more toxic because of delayed vomiting and more prolonged bacterial action.

5. Furthermore, the entire clinical picture, namely, the temperature, pulse, respiratory and blood pressure variations and the general appearance of the patients and the experimental animals, certainly is not that of a toxemia.

6. In addition, the fact that, in uncomplicated cases of experimentally produced intestinal occlusion, the subjects live three or four weeks without food or water or any treatment whatsoever proves definitely that toxemia is not the cause of death.

The experimental workers supporting this theory have attempted to prove it by demonstrating that fluid from closed isolated loops is rapidly fatal when injected intravenously into normal animals. By chemical extraction, they conclude that the toxins are proteoses, nucleoproteins and histamin derivatives. Undoubtedly, intestinal secretions become very toxic when exposed to prolonged bacterial action. Death following intravenous administration, however, proves nothing, since it has long been known that many substances are extremely fatal when introduced directly into the blood stream, whereas if allowed to pass through normal intestinal mucosa their poisonous properties are entirely destroyed. Intravenous peptone injections may cause rapid death, yet the absorption of peptone from the normal intestine is, on the contrary, a natural physiologic process.

Furthermore, the absorption or presence of these toxins in the blood stream has never been demonstrated, nor has the introduction of blood from animals dying from obstruction ever produced untoward symptoms or death.

It is thus evident that, in uncomplicated acute simple obstruction, toxemia is not present, and that death is purely the result of starvation. All injected food and water is quickly vomited, and the result is therefore essentially the same as if these substances had been withheld. Fluid loss through urinary and respiratory excretion is probably similar in both starvation and obstruction. In addition, however, the obstructed animals are losing considerable quantities of the various juices secreted into the gastro-intestinal tract. In the normal starving animal, these fluids are all reabsorbed. Gastric secretory loss, as Pawlow has indicated, is negligible after the fifth day of starvation. Pancreatic juice secretion probably shows a similar inhibition. Intestinal and biliary secretion, however, continues throughout the obstruction period, as indicated by the large quantity of bile stained vomitus. Experiments with biliary, pancreatic and intestinal fistulas show that animals can survive these secretory losses for long periods of time, thus indicating that, in intestinal obstruction, this, in itself, does not cause death but instead merely hastens the starvation process.

That dehydration is very pronounced is evident. The dehydration theory, therefore, contains an element of truth. Fluid loss, however, is only a part of complete starvation for, in the latter, both food and fluids are withheld. Ordinary dogs deprived of all food and water live from fourteen to sixty-six days, with an average of about thirty days, whereas, if allowed water but no food, they may live more than four months. These figures indicate that death in simple obstruction falls within the same period of time as does ordinary starvation. The extra fluid loss in obstruction through vomitus merely accelerates the starvation process.

Furthermore, a review of the tables outlining the experiments on the two starvation dogs shows that changes are exactly similar to those reported for normal starvation animals. The increased viscosity of the blood, the high red cell and hemoglobin figures, the decreased blood volume flow through the extremities, the blood chemistry changes, the extreme loss of body weight and the temperature, pulse and respiratory curves have all been previously reported in starvation experiments.

The statement of Werelius that death in obstruction may be due to hepatic insufficiency and to a large amount of nonperistaltic bowel is not confirmed by our experimental work. Fluoroscopic examination of the proximal segments has always shown very active peristalsis even up to the time of death. That the distal intestine also is not aperistaltic, as generally stated, is proved by the fact that these obstruction dogs frequently pass small quantities of the white pasty feces that accumulate in the distal intestine. The vomitus is always darkly bile tinged and, during the last two weeks, appears to contain a gradually increasing amount of this hepatic secretion. At necropsy the fluid remaining in the proximal intestine is blackish green, and the gallbladder is distended

with black, syrupy bile. Furthermore, blood sugar and urea estimations show no extreme variation from the normal, and the clotting time, instead of being increased, is, on the contrary, markedly decreased. Aperistalsis and ahepatism seem to play no rôle in acute obstruction death.

Experiments with obstructed mucosal extract have never warranted serious consideration.

Haden and Orr [10] state that, in high, simple intestinal obstruction, the characteristic changes in blood chemistry are a fall in chlorids, an increase in nonprotein nitrogen and, usually, an increase in the carbon dioxid combining power of the plasma. Since the nonprotein nitrogen increase does not begin until after the chlorids are well depleted, they conclude that the chlorids act as detoxicating agents. They also assume that the toxins are absorbed from the intestinal tract, and suggest that they cause much tissue destruction. An examination of their protocols shows that most of their dogs died within from two to five days after the obstruction was produced, namely, during the healing period, unless treated by subcutaneous saline injection. Their conclusion, therefore, as to characteristic blood chemistry changes, toxin, absorption and tissue destruction appears unwarranted. On the contrary, we find that the blood chemistry changes in untreated, uncomplicated, simple obstruction dogs are almost identical with those reported by Morgulis and Edwards [9] for complete food and water starvation. The chlorids, instead of being decreased, remain normal or show a slight increase. The nonprotein nitrogen increases in the same ratio as that occurring in starvation. The carbon dioxid combining power of the plasma varies considerably, usually somewhat above the normal limits.

CONCLUSIONS

1. Death in uncomplicated cases of acute intestinal obstruction is due to starvation.

2. The blood chemistry changes noted in uncomplicated simple intestinal obstruction are almost identical with those found in complete starvation. Hypochloremia is not present.

3. Dehydration, in uncomplicated cases of simple intestinal obstruction, is usually very pronounced.

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10. Haden, R. L., and Orr, T. G.: Effect of Inorganic Salts on the Chemical Changes in the Blood of the Dog After Obstruction of the Duodenum, J. Exper. Med. **39**:321 (Feb.) 1924.

INTARVIN IN DIABETES*

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For the last three years, I have been feeding intarvin to diabetic patients and wish here to report the results thus far obtained. Most likely, this series of cases is the largest treated in this manner in one clinic.

Before I discuss the effects of intarvin, it is perhaps advisable briefly to review the rationale of this treatment.

Intarvin is the glyceryl ester of margaric acid. Its chemical formula is $(C_{16}H_{33}COO)_3\ CH_2.CH.CH_2$. We synthesized it in edible form in our laboratory. The theory underlying the therapeutic value of intarvin is, briefly, as follows:

In the wake of the intolerance for starchy foods that the diabetic patient evinces, there follows a disturbance in the assimilation of the fat foods, and this derangement is still more dangerous to the patient.

How do fats break down in the body?

It was shown by Knoop,[1] in 1905, that when fatty acids are given to animals in combination with aromatic radicals they are oxidized in a definite manner in the animal organism. It is known that if benzoic acid is administered by mouth it is excreted in the urine in conjunction with amino-acetic acid as hippuric acid.

If a higher acid than acetic acid is administered, the resultant product eliminated is either the hippuric acid or the phenaceturic acid, depending on whether the side chain was of an odd or even number of carbon atoms. Knoop, therefore, concluded that, in the oxidation of fats, the beta-carbon atom was oxidized and that two carbon atoms dropped from the chain together. This view was supported by Dakin's discovery that when phenyl propionic acid was given in large amount phenyl beta-oxypropionic acid was detected in the urine.

In his excellent summary, "Physiological Oxidations," Dakin[2] reviews the modern status of the theory of oxidation of fatty acids. I quote from him:

> In spite of a good many vigorous onslaughts, the theory of beta-oxidation applied to fatty acids as put forward originally by Knoop has held its own. It will be recalled that one of the main supports of Knoop's views was furnished by Embden's observation that the normal fatty acids containing an even number of carbon atoms, varying from 4 to 12, all gave rise to aceto-acetic acid when their

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1. Knoop, F.: Beitr. z. chem. Phys. u. Path. **6**:150, 1914.
2. Dakin, H. D.: Physiol. Rev. **1**:406 (July) 1921.

salts were perfused through a surviving liver. The normal fatty acids containing an uneven number of carbon atoms failed to cause any increase in aceto-acetic acid production. An interesting clue to the probable fate of some of these normal fatty acids has been furnished by Ringer, who finds that propionic acid is practically quantitatively converted into glucose in the phloridzinized dog and that normal valeric and heptylic acids given an amount of glucose under similar conditions comparable to the amount of propionic acid they might yield through beta-oxidation:

$CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.COOH$ $CH_3.CH_2.CH_2.CH_2.COOH$ $CH_3.CH_2.COOH$

Blum and Woringer have recently shown that when propionic acid is given to normal dogs and rabbits, lactic and pyruvic acids are excreted, and these undoubtedly represent intermediary products of the oxidation of propionic acid, although it is not clear as to which of these two acids is first formed or whether perchance they are formed from acrylic acid, which Schwenken has shown to be almost quantitatively converted into glucose in the phloridzinized dog. The conversion of propionic acid into lactic acid explains the conversion of the former acid into glucose in the phloridzinized animal, for as is well known, the conversion of lactic acid into glucose under these conditions is virtually quantitative. The formation of lactic and pyruvic acids from propionic acid must be regarded as a case of alpha-oxidation, though possibly indirect, but since normal beta-oxidation with formation of ketonic acid is no longer possible with a three-carbon acid it need not be regarded as violating the beta-oxidation rule applicable to acids containing four or more carbon atoms. It appears, therefore, that in the metabolism of normal fatty acids containing four or more carbon atoms aceto-acetic acid is a common metabolite of all those with an even number of carbon atoms, while lactic acid is common to those with an uneven number.

In the catabolism of fats (under normal conditions, that is, in the presence of proper carbohydrate oxidation) there is a rapid breakdown of the fatty acid radical to the four-carbon acid, i. e., butyric acid:

$$\begin{array}{ll} CH_2\text{-}OOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R & COOH \\ CH\text{-}OOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R & CH_2 \\ CH_2\text{-}OOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}R & CH_2 \\ & CH_3 \end{array}$$

The butyric acid is then rapidly catabolized to carbon dioxid and water.

This process, however, is markedly disturbed in states of deficient carbohydrate oxidation. In the latter circumstance, the fats are primarily broken down to butyric acid, as in the normal condition, but, in the absence of the heat of carbohydrate consumption, the further decomposition of the butyric acid proceeds very slowly. The butyric acid, under these conditions, is decomposed first to beta-oxybutyric acid and then to aceto-acetic (or diacetic) acid. The further decomposition to acetone takes place very largely in the urine itself.

$COOH.CH_2.CH_2.CH_3$	$COOH.CH_2.CHOH.CH_3$	$COOH.CH_2.CO.CH_3$	$CH_3.CO.CH_3$
I. Butyric acid	II. B. Oxybutyric	III. Aceto-acetic	IV. Acetone

Rosenfeld [3] has said that fats burn only in the fires of carbohydrates, but this is not quite right, as only the breakdown of the lowest products of fat decomposition, that is to say, the acetone substances, depends on the catabolism of the carbohydrates.

3. Rosenfeld, Genia: Biochem. Ztschr. **109**:250, 1920.

How does the fat decompose to butyric acid? Of the two components of fat, only the fatty acids yield the ketone substances. The glycerin portion of the fat molecule is antiketogenic in nature.

Magnus-Levy says:

> By investigations performed either with living beings in a state of acidosis or with the transfused dog's liver, it has been established that fatty acids are broken down by a repeated splitting off of two carbon atoms. The first step is the formation of the beta-oxybutyric acid, which is then transformed to the beta-keto acid:
>
> $COOH.CH_2.CH_2.CH_3$::R $COOH.CH_2.CHOH$::::B-oxy acid $COOH.CH.CO$::::B-keto acid
>
> The transformation requires a twofold oxidation at the beta-carbon atom. Contrary to what happens in the lungs with aceto-acetic acid, a splitting off of the carboxyl group and the formation of true ketone generally does not take place in the metabolism; instead we find a simultaneous splitting off of the carboxyl group and of the alpha-carbon atoms, thus yielding a new fatty acid lower by two carbon atoms.

Embden [4] has found that only fatty acids of an even number of carbon atoms will yield aceto-acetic acid in the transfused dog's liver. In this way, from stearic acid (C_{18}), palmitic acid (C_{16}) is formed; from this an acid with 14, 12, 10 or 8 carbon atoms is derived. Then caproic acid (C_6) and, finally, butyric and oxybutyric acids are formed.

Several years ago, I endeavored to see the effect of the feeding of a fat containing an odd carbon fatty acid.

We have succeeded in preparing an odd carbon fatty acid fat that is edible, is absorbed to the extent of about 90 per cent., is catabolized in the body and does not yield the ketone substances derived from butyric acid.

The method of preparation is as follows: Stearic acid has its acid group substituted by an organic radical and on oxidation with a strong oxidizing mixture that C_{17} acid ($C_{16}H_{33}COOH$, margaric acid) is produced. This is easily purified and then united with glycerol to form a neutral fat.

This fat, when well prepared, is of a white creamy color, odorless and tasteless, melting at 38 C., and is neutral in reaction. When cold and granulated, it is quite palatable. It does not cause any sense of nausea, and it seems to satisfy the hungry craving for fat that diabetic patients have. A number of patients were fed the fat, but it will be sufficient to describe three cases, as the results are typical.

Intarvin was sent to many responsible laboratory and clinical workers, and the results thus far obtained may be summarized as follows:

1. It is absorbed (Benedict and West [5]).

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4. Embden, G.; Salomon, H., and Schmidt, F.: Beitr. z. chem. Phys. u. Path. **8**:129, 1908. Embden, G., and Marx, A.: Ibid. **9**:318, 1908.

5. Benedict, E., and West, R.: Proc. Soc. Exper. Biol. & Med. **21**, 1924.

2. It is nontoxic (Heft, Kahn and Gies [6]).

3. It is nutritious and substitutes, so far as nourishment goes, for natural fats (Gies, Baehr, Lundin,[7] Modern [8]).

4. It is catabolized without the production of the acetone substances (Kahn,[9] Hubbard,[10] McCann, Sansum, Lundin,[7] Modern [8]).

5. In the phloridzinized dog, it was transformed to glucose. This is not the case in diabetic subjects. Benedict and West [5] did not find it changed to glucose in phloridzinized dogs.

6. What the end products of the catabolism of intarvin are is a mooted point.

Intarvin is easily absorbed. Analysis of the feces of a normal person showed 5 per cent. loss, indicating in that case an absorption of 95 per cent. In general, the absorption varies between 90 and 95 per cent.

Prof. S. H. Gage of Cornell University has measured the absorption by examination of the blood. He reports the exact figures he has obtained, which show rather good absorption.

Dr. George Baehr of Mount Sinai Hospital reports to me as follows:

> These observations were made on four patients in whom, during the period of intarvin administration and absence of acetonuria, we were able to demonstrate by respiratory quotient determinations and other means, that they were burning an amount of carbohydrate inadequate to secure complete combustion of the fat, that is, if the total fat metabolized had been of the even carbon variety.

It is nontoxic and is capable of sustaining life like natural fat. Prof. William J. Gies and Dr. H. L. Heft of Columbia University have substituted this fat for natural fat, in feeding experiments on rats. The rats behaved normally; their weight increase did not vary from the controls. They gave birth to new litters who again were fed this fat. In this way, four generations of rats, all normal and all behaving normally, have thus far been reared.

When intarvin is administered to phloridzinized dogs, it is excreted as glucose. Prof. Graham Lusk of Cornell University has made one such experiment, and has reported this observation to me. This is in confirmation of the work done by Dr. Lusk and his assistants, Ringer and others. They have repeatedly reported that an odd carbon fatty acid fat fed to a phlorhizinized dog is excreted as glucose. The acid is broken down gradually to the C_3 acid (propionic acid), which is then converted to glucose.

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6. Heft, Kahn and Gies: Proc. Soc. Exper. Biol. & Med. **21**:479, 1924.
7. Lundin, H.: J. Metabolic Research **4**:157, 1923.
8. Modern, F. S.: J. Metabolic Research **4**:177, 1923.
9. Kahn, M.: Proc. Exper. Biol. & Med. **19**:265, 1922; ibid. **21**:31, 1923; Am. J. M. Sc. **166**:826 (Dec.) 1923.
10. Hubbard and Wright: Proc. Soc. Exper. Biol. & Med. **21**:70, 1924.

This conversion to glucose does not take place in pancreatomized dogs nor in diabetic patients, again demonstrating the great difference between phlorhizin glycosuria and true diabetes.

Dr. Sansum of the Potter Metabolic Clinic, Santa Barbara, Calif., draws the following conclusions from his experiments on intarvin. I shall conclude my paper by quoting these sentences.

1. Intarvin, unlike natural fat, may be used in the diet of a patient with severe diabetes without fear of acidosis.

2. The substitution of natural fat for intarvin in the amounts used in the experiment promptly brought on an alarming acidosis.

3. The foregoing severe acidosis was promptly relieved when the intarvin was restored to the diet.

Gies and Heft, in collaboration with me,[8] report as follows:

Eight normal, female rats from one litter were originally separated into groups of four. One of two males, of practically the same size and vigor from an unrelated litter, was added to each of these two groups. One group received a balanced natural diet with a definite proportion of intarvin mixed with the meat ration. The other group received the same natural diet under identical conditions, with rendered lamb fat instead of intarvin added to it. In each successive generation, thereafter, the maternal rats that received intarvin were selected from the direct descendants of those that had previously been given the "intarvinated" diet. The control maternal rats in each generation in a series were selected from the direct descendants of those that received a diet containing an addition of lamb fat. The paternal rats in each generation (unrelated to the females) were selected on the same dietary basis as that for the maternal, or from litters on the ordinary diet without addition of fatty matter.

Rats have been carried, in this parallel way, into the fourth generation in one series and into the third generation in another. (The experiments are in progress, and litters in the fifth and fourth generations, respectively, will soon be available). There has been no discernible effect on the animals thus treated, or on their fecundity. The animals in the third and fourth generations appear to be as completely normal as those with which the tests were started last August.

The tissues of many of the rats have been used in the studies of the absorption and distribution of glyceryl trimargarate.

Hubbard and Wright have obtained the following results. I shall quote several of their sentences.

Haldane has shown that if large doses of sodium bicarbonate (0.6 gm. per kilogram of body weight) are fed to normal subjects receiving normal diets the metabolism of glucose is depressed and acetone bodies appear in the urine. An experiment was planned to determine whether an increased excretion of acetone could be induced by moderate doses of the alkali in an arthritic subject who was receiving a diet which furnished sufficient calories for her needs (the patient gained in weight during the period of study) but which contained such small amounts of carbohydrate as just to prevent any significant ketosis. A markedly increased excretion of acetone was induced by 1.3 gm. (20 grains) of sodium bicarbonate fed in three equal doses after each meal. The increased excretion lasted as long as the drug was continued (from August 11 to 18). The diet was approximately constant throughout the experiment except on the 17th and 18th of August, when the carbohydrate was somewhat decreased

through an error. After this experiment part of the fat in the diet was replaced by a synthetic fat containing fatty acids with an odd number of carbon atoms (intarvin). A reduction in the amount of acetone excreted was found on the 22d and the 23d, as would be expected from the work of Kahn. The carbohydrate content of the diet was then slightly decreased, and again intarvin was substituted for part of the fat (August 28) and an even greater decrease in the excretion of acetone than before was found. In this experiment on a subject maintained at the borderline of ketosis, therapeutic doses of sodium bicarbonate caused an increased, and the synthetic fat intarvin a decreased excretion of acetone.

Lundin[7] and Modern[8] confirmed my results as to the non-production of acetone substances from intarvin. The results they have otherwise obtained are highly interesting, if not illuminating, and my critique of their work will appear in the *Journal of Metabolic Research*.

In feeding intarvin, the following plan is followed: The diet of the patient is determined according to the conventional method, i. e., it is determined how many grams of fats, carbohydrates and protein the patient can take in without the formation of acetone or the excretion of glucose in the urine. If the patient needs insulin, it is administered to him according to the orthodox system, after the proper diet for such a subject has been computed.

Now, having administered this proper diet of *natural* fats, carbohydrates and proteins, the caloric value yielded is calculated, and to this value is added a sufficient weight of *artificial* fat (intarvin) to bring up the caloric intake to a good maintenance diet. Thus, for example, if a patient without insulin can only take in 800 calories a day, and with insulin 1,800 calories a day, intarvin may be added to bring up the caloric intake to say 2,500 calories a day. If a patient, for any reason, does not receive insulin (whether insulin has no effect, or the patient does not require insulin, or refuses to take it), a quantity of intarvin may be added sufficient to make the tolerance diet a maintenance diet.

Intarvin may be administered in any form. It has been reported to me that exposure of intarvin in a plate to the direct rays of the sun takes away its flavor (slight as it is). I have found that it can easily be taken dissolved in hot black coffee or tea. If the physician does not impress the patient with a psychologic distaste, the patient will not observe any disagreeable flavor or odor. It surely is more tasteful than any emulsion of cod liver oil.

SUMMARY

The results obtained in patients may be summarized as follows:

1. It nourishes them, so that they gain weight.

2. It allays their sense of hunger.

3. It strengthens them, so that they do not feel so "weak and tired," the usual complaint of the diabetic patient.

4. It never produces ketosis, i. e., beta-oxybutyric acid, diacetic acid or acetone.

5. It never produced acidosia. This I have determined in more than 100 cases by examination of the blood for the carbon dioxid combining power.

6. It never yields glucose.

7. Many more patients can be treated with intarvin, and thus insulin can be preserved for the patients with very severe diabetes who really need it.

METHODS OF RECOGNIZING SCAPULAR TYPES IN THE LIVING*

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My investigations[1] led to the classification of scapulae (convex, straight and concave), and brought the scapula into definite relation with a number of biologic problems. Among these may be mentioned: morphogenesis and ontogenesis in general; bone growth; bone form and variation in man and other vertebrates; the modification of bones by muscle attachments, muscle pull and various environmental influences in prenatal and postnatal periods; age changes in bone and other tissues; human heredity; human longevity; human morbidity, and human adaptability in general. The relations of the scapula to the foregoing problems and the desirability of establishing uniform and dependable methods of recognizing scapular types in the living are shown by recalling some recent findings.

SUMMARY OF SOME RECENT FINDINGS

1. Some recent findings are: Similar scapular types are present in varying degrees and percentages in the skeletal remains of all accessible human races and stocks both ancient and modern.

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1. Graves, W. W.: The Scaphoid Scapula; A Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance, Med. Rec. **78**:861-873, 1910; The Clinical Recognition of the Scaphoid Type of Scapula and Some of Its Correlations, J. A. M. A. **55**:12-17 (July 2) 1910; Some Remarks on the Scaphoid Scapula and Its Syndrome, Tr. Nat. A. Study of Epilepsy **8**:56 (June 16) 1911; The Scaphoid Scapula Syndrome; Its Connection with Syphilis in the Ascendants, Interstate M. J. **18**:109-116, 1911; also translated in Deutsche Ztschr. f. Nervenh. **41**:247-257, 1911; Scapula scapoidaea, eine häufig vorkommende Anomalie des Schulterblattes, ihr Zusammenhang mit Syphilis in der Aszendenz, Med. Klin. **7**:208-301, 1911; Einige Bemerkungen über die Scaphoidskapula und ihre Begleiterscheinungen, Wien. klin. Wchnschr. **25**:245-238, 1912; Remarks on the Scaphoid and Its Syndrome; the Connection with Syphilis in the Ascendants, J. Cutan. Dis. incl. Syph. **31**:241-245, 1913; The Age Incidence of the Scaphoid Type of Scapula: Its Bearing upon Problems of Racial Morbidity, Contributions to Medical and Biologic Research, New York, Paul B. Hoeber, **1**:525-532, 1919; An Appeal for Embryos and Fetuses, J. A. M. A. **73**:1788 (Dec. 6) 1919; Discussion: The Scaphoid Type of Scapula, Am. J. Syph. **4**:478, 1920; The Types of Scapulae: A Comparative Study of Some Correlated Characters in Human Scapulae, Am. J. Phys. Anthropol. **4**:3, 1921; Observation on Age Changes in the Scapula; a Preliminary Note, Am. J. Phys. Anthropol. **5**:21, 1922; The Age Incidence of Scapular Types: Its Possible Relation to Longevity, Tr. Am. A. Life Insurance Medical Directors, 1923; The Relations of Scapular Types to Problems of Human Heredity, Longevity, Morbidity and Adaptability in General, Arch. Int. Med. **34**:1-26 (July) 1924; German translation in Ztschr. f. Konstitutionslehre, to be published.

2. Scapular types are inherited morphologic features, and with the exception of definite racial marks of inheritance, in no accessible morphologic feature common to "normal" human inheritance thus far known do the members of a given generation more closely and more frequently resemble each other and at the same time one or both parents than they do in scapular types.

3. In the tenth to twelfth fetal week the human scapula has attained the general form it apparently ever afterward retains, and in this early period of development the same scapular types are found as in all subsequent periods of prenatal and postnatal existence.

4. In prenatal and postnatal periods one finds scapular type asymmetries, "mixed types," in the same person. These may be convex on one side and on the other concave, or convex on the one side and straight on the other, or straight on one side and concave on the other. Such asymmetries in type are independent of right or left-handedness, occupation, disease or other environmental influences. Moreover, similar mixed types are found in some other mammals.

5. In all postnatal periods of life, each scapular type (convex, straight and concave) is found in varying degrees and percentages, regardless of race, stock, sex, social level, occupation and environment. They are found in the tall, the short, the fat, the lean, the "broad backs," the "narrow backs," the weak, the strong, the healthy, the sick, the near to, and the remote from, an ideal in development, the mentally brilliant, the average and the defective, the well and the poorly muscled, the "excellent," the "good" and the "poor" types, and in all heretofore described human types.

6. It is among persons disclosing innate defectiveness in adaptation, those disclosing definite asymmetries, disproportions and disharmonies in total make-up, that the straight and concave types are most frequently found.

7. Investigations of various groups of human beings representing living, necropsy and skeletal material of known age disclose a finding as yet unparalleled in mammalian morphogenesis, *the age incidence of scapular types;* that is, it has been found that the convex increases while the straight and concave decrease in frequency of occurrence during successive age periods from birth to old age.

8. It also has been found that no process or circumstance as yet known changes one scapular type into another after the earliest type formation; hence the inference is tenable that the straight and concave are more often found than are the convex in the plus potentially sick, the shorter lived of the race.

From the foregoing summary it becomes apparent that the human scapula has definite relations to the problems mentioned and particularly

to those of human heredity, morbidity, longevity and adaptability in general. These are vital, practical and enduring problems, requiring universal and continued research. They are enduring because they are founded in differences and similarities (variations) apparent in the individuals of various species, and in none more so than in the human.

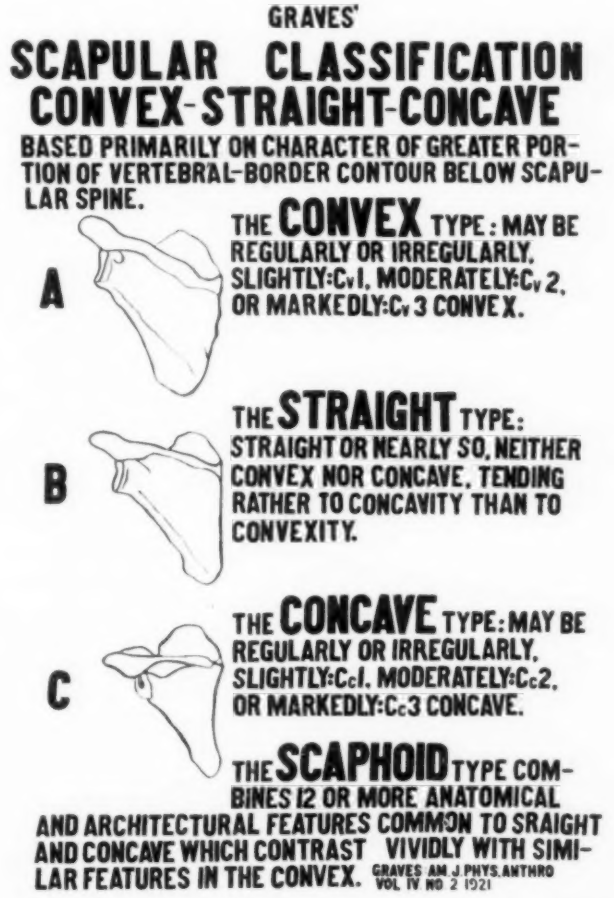
GRAVES'
SCAPULAR CLASSIFICATION
CONVEX-STRAIGHT-CONCAVE
BASED PRIMARILY ON CHARACTER OF GREATER PORTION OF VERTEBRAL-BORDER CONTOUR BELOW SCAPULAR SPINE.
A
THE CONVEX TYPE: MAY BE REGULARLY OR IRREGULARLY. SLIGHTLY: Cv 1. MODERATELY: Cv 2. OR MARKEDLY: Cv 3 CONVEX.
B
THE STRAIGHT TYPE: STRAIGHT OR NEARLY SO, NEITHER CONVEX NOR CONCAVE, TENDING RATHER TO CONCAVITY THAN TO CONVEXITY.
C
THE CONCAVE TYPE: MAY BE REGULARLY OR IRREGULARLY. SLIGHTLY: Cc 1. MODERATELY: Cc 2. OR MARKEDLY: Cc 3 CONCAVE.
THE SCAPHOID TYPE COMBINES 12 OR MORE ANATOMICAL AND ARCHITECTURAL FEATURES COMMON TO SRAIGHT AND CONCAVE WHICH CONTRAST VIVIDLY WITH SIMILAR FEATURES IN THE CONVEX.
GRAVES AM J PHYS ANTHRO VOL IV NO 2 1921

Fig. 1.—Scapular types; drawings by P. A. Conrath. *A*, convex type (Cv2); *B*, straight scaphoid type (St.), and *C*, concave scaphoid type (Cc3).

The helpfulness of scapular classification in the prosecution of these problems will depend on the ease and reliability with which scapular types can be recognized in skeletal and living material. It is therefore the prime purpose of this article to point out dependable methods applicable to the living. This seems all the more necessary since the

recognition of scapular types represents a phase of the physical examination unknown prior to the classification of scapulae in 1910.

BASES OF SCAPULAR CLASSIFICATION

Probably no bone in the body discloses as many morphologic and architectural characters as the scapula. Each of these characters shows a range in variation, but none a wider range than the vertebral border below the scapular spine. The variation-range of this part of the bone is from extremely convex to extremely concave or vice versa. Consideration of this fact enables one to classify the scapulae of various human races and stocks and of some other mammals into convex, straight and concave types. The classification of scapulae in human skeletal and living material is based primarily on the character of the greater portion of the vertebral border contour below the scapular spine in its relation to a straight line. By "greater portion" is meant the contour of the vertebral border between its point of mergence with the scapular spine and a point where it merges with the inferior angle region. The contour of the "greater portion" of this part of the vertebral border may be regularly, irregularly, slightly, moderately or markedly convex or concave, or it may be straight or nearly so, tending rather to concavity than to convexity. The classification is based secondarily on an assemblage of variations peculiar to, or most frequently found in, each type. Thus one type of scapula is brought into more or less sharp contrast with the other types not only by the character of the vertebral border contour (convex, straight or concave) but also by a number of correlated characters. While each scapular type embodies a variable constellation of correlated characters, it is nevertheless the relation of the contour of the greater portion of the vertebral border below the scapular spine to a straight line that establishes a firm foundation for scapular classification in skeletal and living human material. Figure 1 summarizes and pictures the primary basis of scapular classification and suggests useful symbols in recording the types and varying degrees of convexity and concavity.

METHODS APPLICABLE TO THE LIVING

It is a principle in clinical medicine and anthropometry to measure everything that can be measured with instruments of precision, but some of our most important findings are secured by comparing things and by exercising our powers of observation. It is with such methods that scapular classification must in the main be made. In approximately 6,000 skeletal scapulae, I have found only twenty-two mature bones, less than 0.5 per cent., in which classification was doubtful or impossible. As it depends on the factors of age, mental state, the nature of the

material and the personal equation, classification is obviously more frequently doubtful or impossible in the living. The methods applicable to the living are founded on the proper use of inspection, palpation and roentgen ray. In any part of the physical examination, the subject must be capable in some measure of cooperating with the examiner; hence the age or mental state of the person may wholly prevent classification or render it uncertain. In subjects under 3 years and especially in infants, in the definitely feeble-minded in all ages, in epileptics and dements, and in negativistic, resistive and excited insane, scapular classification is found to be difficult or doubtful in many and impossible in some. In the very obese in any period of life, classification can never be accurate, except with the aid of the roentgen ray. Accuracy even with this method depends on the use of proper precautions in minimizing or in preventing shadow distortion. To these ends, if the fluoroscopic examination is made, the subject should stand squarely before the target while the fluoroscope is placed squarely over the scapular region. To secure a reliable picture, the subject should rest with the scapular region squarely on the plate with the arms close to the sides and the forearms in positions of moderate supination. The exposure should be made while the subject holds his breath at the end of a deep inspiration. Prior to the sixteenth year of life, the roentgen ray is not dependable because the vertebral border and the inferior angle regions are still mainly cartilaginous, and the vertebral border cartilage is practically transparent to the ray in the living.

Depending on the age, mental state and nature of the material encountered the difficulties in scapular classification are very real, but they are practically negligible with proper methods under normal conditions. There is, however, another difficulty common to every phase of the physical examination, whether made with instruments of precision or other means, and this is the personal equation. The use of proper methods reduces this difficulty to a minimum, but it can never be wholly eliminated as long as the physical examination must be made with the imperfect mechanisms common to human beings. It is only by being conscious at all times of one's own imperfections and of the sources of error that one may secure results in scapular classification comparable in accuracy to other phases of the physical examination. It is in carefully carrying out the methods of inspection and palpation in orderly sequence, remembering the sources of error, and in utilizing certain bodily correlations of scapular types that the personal equation with these methods can be reduced to a minimum and a high degree of accuracy can be secured. Let us now direct our attention to some of the bodily correlations of scapular types and to avoidable pitfalls in classifying them when inspection and palpation are employed.

Inspection.—Classification by whatever method should never be attempted through the clothing. While the subject is stripped at least to the waist line and standing at ease with the shoulder girdle muscles relaxed and in good illumination, one should note the general development, the bodily habitus and attitudes, the topography of the trunk and abdomen, the form of the chest, the course of the clavicles, the right and left acromial level (height), the length of the neck, the spinal curves, the general muscular development, the dimensions and form of the interscapular space and the relation of the vertebral borders to the vertebral axis. In noting these points, one cannot avoid seeing others, such as nearness to, and remoteness from, good degrees of symmetry, proportion and harmony of the entire physical make-up, and variations about the skull, face and other parts of the body. All of these are helpful in the recognition of scapular types. During inspection of a number of persons, one quickly becomes aware of variations more frequently associated with one scapular type than with others, not only in the parts but in the total make-up of the subject. Among the variations that appear to be more frequently correlated with straight, and especially concave, than with convex types are: rather sluggish bodily attitudes; "narrow back" habitus; meager or moderate musculature; long neck; drooped, hanging or rounded shoulders; chicken and funnel-shaped chest; long and flat chest often unduly flattened about the upper third anteriorly either unilaterally or bilaterally; narrowness of the costosternal angle; a horizontal or transverse course of one or both clavicles; prominent sternoclavicular and acromioclavicular joints; postural spinal curves of varying nature and degree; a difference in acromial level, and the relatively frequent finding of a flattened or retracted appearance of the upper third of the chest anteriorly on the low shoulder side. Moreover, one seldom finds in any age period Cc2 in "broad backs," but Cc2 and Cc3 types are relatively frequent findings in "narrow backs" prior to the fiftieth year of life.

The modeling of the vertebral border below the scapular spine is readily seen, except in the obese and the unusually well muscled. One frequently notes that the vertebral borders and the inferior angles are prominent (winglike), and these findings may be present in any type, but "winging" is more frequently associated with straight and concave types than with the convex (Figs. 2 and 3).

Differences in dimension and form of the interscapular space are, in themselves, often dependable signs of type. The interscapular space is usually narrowed in the convex and widened in the straight and in the concave because the average of each of three scapular indices is less in the straight and in the concave than in the convex (Figs. 2 and 3). Usually in the convex the form of the space is roughly A shaped; the general

direction of the vertebral border is downward and lateralward, and the inferior angle of each bone is then from 1 to 4 cm. further away from the vertebral axis than is the base of the scapular spine (Fig. 2*A*; Fig. 3*B*). In the straight or concave, the base of the scapular spine

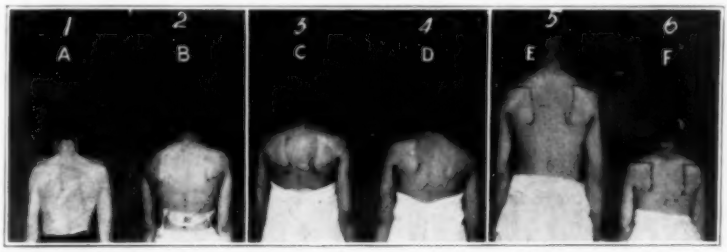

Fig. 2.—*C* and *D* are sisters, *E* and *F*, brother and sister; all subjects are standing at ease, shoulder girdle muscles relaxed, showing modeling of each vertebral border contour below the spine and the dimension and form of each interscapular space. Narrowness of space in *A* should be noted, broadness in *B*, *C*, *D*, *E* and *F*. The space is A-shaped in *A*, H-shaped in *B* and *F*, V-shaped in *C*, *D* and *E*. *D* has the Cc2 type on the left and the Cc3 on the right, and the right shoulder is definitely lower than the left. The other subjects have symmetrical types, and the shoulders of each are approximately equal in height.

Fig 3.—Subjects standing at ease, shoulder girdle muscles relaxed showing modeling of vertebral border contour below spine. Broadness of interscapular space should be noted in *A* and narrowness in *B* and *C*. The space is A-shaped in *B*, H-shaped in *A* and *C*. *C* has Cv2 type on the left and Cv1 on the right, and the right shoulder is lower than the left. *A* has the straight type on the right and the left; *B* has Cv2 type on the right and the left, and the shoulders of each are approximately equal in height.

and the inferior angle are usually equidistant, or nearly so, from the vertebral axis and the form of the interscapular space is H shaped. The borders are parallel, or nearly so, to the vertebral axis (Fig. 2*B* and *F*; Fig. 3*A*). In some instances, however, in any type but more fre-

quently in the straight and concave, it is roughly V shaped. The general direction of each vertebral border is then downward and medialward (Fig. 2*C*, *D* and *E*).

Another point as an aid to accuracy in scapular classification is the difference frequently noted in the acromial level (height), left and right. This difference has long been recognized especially by non-professional observers, and it is commonly believed to be due to previous or present disease or injury or occupation. The most frequent cause, however, appears to be differences in degree of what I [2] have elsewhere called the long scapular-axis-spinal angle, i. e., the outer inferior angle formed by the long scapular axis and the scapular spine. This angle is

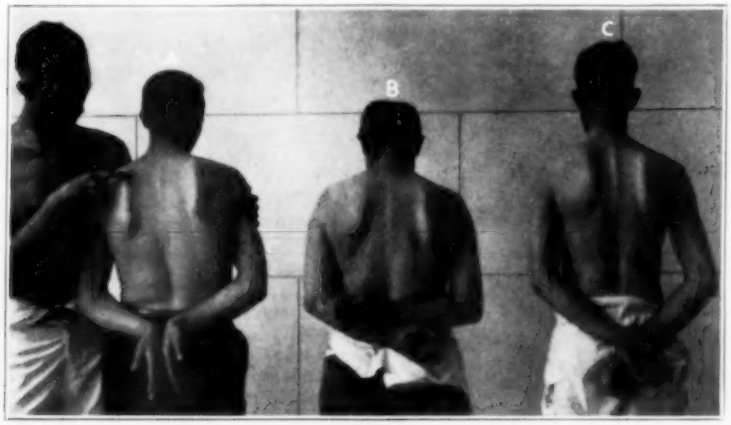

Fig. 4.—Same subjects as shown in Figure 3 in three useful upper extremity postures to relax rhomboid, trapezius and serratus muscles. Such postures render the vertebral borders more prominent for inspection and palpation. The person at the left is locating the base of the scapular spine.

usually definitely obtuse in the convex and more nearly a right angle in the straight and concave types. Thus, if a living subject possesses a convex on the right and a straight or concave on the left, the acromial level is usually lower on the left than on the right. The correlation of the varying degrees of this angle is not only present in subjects possessing one type of scapula on one side and another type on the other, but it is also present in subjects having differences in degree of a type. For instance, if the left scapula is Cv3 and the right Cv1 or 2, the right is usually lower than the left (Fig. 3*C*). Similarly, if the right scapula is Cc3 and the left Cc1 or 2, the left shoulder is usually lower. Marked differences in acromial level are most frequently found in subjects possessing on one side a convex and on the other a

2. Graves (Footnote 1, eleventh reference).

concave. But these differences are seldom missing in persons who have straight on one side and concave on the other and in those having different degrees of concave types (Fig. 2*D*), or of convex types (Fig. 3*C*). The differentiation of one type from the others and the determination of the varying degrees of convexness and concaveness can come only from combining inspection and palpation and in the obese from using the roentgen ray.

Fig. 5.—*B* and *A* shown in Figures 3 and 4; *B* is bringing lateral pressure to bear on the shoulder girdle of *A*, rendering the vertebral border still more prominent for inspection and palpation and testing relaxation by placing the side of the hand somewhat beneath the vertebral border.

Palpation.—The subject should stand at ease in natural attitudes without tensing any of his muscles, and particularly those of the shoulder girdle. During palpation, the examiner should neither see nor feel contractions of these muscles and especially not of the rhomboid and the trapezius. If contractions are seen or felt during palpation, the findings may be faulty; for example, a straight or a moderately concave may be called a convex. These muscles are usually in a good state of relaxation when the patient stands at ease, but they can be further relaxed by certain upper extremity postures, for instance, by crossing

the subject's pronated hands over the sacrum or by placing the forearms over the small of the back, or by approximating the backs of the wrists over the small of the back (Fig. 4). Posturing the upper extremities in any of these positions renders the border contours more prominent for inspection and palpation. In such postures the serratus anterior muscles become relaxed, and the relaxation of these muscles is a further aid in rendering the vertebral borders prominent.

To secure greater muscular relaxation, thereby rendering the vertebral borders still more prominent, i. e., further elevating them from the chest wall, the following method is recommended: If the examiner is right-handed, he should face and stand close to the left side of the subject, place his left hand over the upper portion of subject's right arm and bring rather firm pressure to bear on the subject's shoulder girdle regions between his own left arm and chest (Fig. 5). With complete relaxation secured, one can now readily place the side of the hand or finger tips somewhat beneath each vertebral border (Fig. 5). If one can do this, he can then be sure that he has secured the desired relaxation of the rhomboid, trapezius and serratus muscles. Having located the base of the scapular spine and the inferior angle, palpation should now be made of the vertebral border contour throughout its extent below the spine. The palpating fingers should be held at a right angle, or nearly so, to the border. Palpation should be made slowly and firmly and without pain or discomfort to the subject. Undue haste or force defeats proper palpation by exciting muscle contraction and resistance. One should not only palpate under control of vision for convexness, straightness or concaveness of the "greater portion," but also for the minutest variations along the border contour.

It is helpful to study border contour variations in good photographs of bones or, better still, in bones. Some of these variations may be confusing to the beginner, and should here be mentioned. Vertebral border contours uniformly or regularly smooth, uniformly or regularly convex, straight or concave are not usual findings. The contour is more often somewhat uneven or irregular in convexness, straightness or concaveness. In any type but especially in the straight and slightly concave, the border contour is often broken by one or more "buds" or "processes," varying in size and location. A frequent finding in the straight and an occasional finding in the concave is a vertebral border prominence variable in size just above the inferior angle. A relatively frequent finding, especially in convex types, is a concavity of variable depth and length at the base of the scapular spine or just above the inferior angle. In either case, the greater portion is usually convex in some degree. In any border contour presenting a concavity in both locations, the intervening part representing the "greater portion" is also usually convex in

some degree. The greatest degree of convexness or concaveness may be found in the upper, middle or lower third of the border. The foregoing relatively common minor variations should lead to but little confusion if one constantly remembers the primary basis of scapular classification—the character of the greater portion of the vetebral border contour below the scapular spine in its relation to a straight line. The classification of each scapula should be determined, also the degree if found to be convex or concave, and the findings recorded. A record should also be kept of those cases in which scapular classification is found to be impossible and the reason for nonclassification should be stated . . . whether obese, resistant or anatomic. (For methods of recording and tabulating scapular types the last reference in Footnote 1 should be studied.)

COMMENT

I have here given methods of recognizing scapular types in the living which I have found to be dependable, and have pointed out a few helpful bodily correlations and some pitfalls of error. It is believed that these methods will enable others who have proper training in clinical medicine to develop an accurate technic and to reduce the personal equation to a minimum. These are prime purposes in the application of every method, medical or otherwise. The work of others in similar material and in similar age periods in scapular classification has yielded very similar percentages to those secured by me. These results indicate that the difficulties in scapular classification in suitable material plus the personal equation should not yield a total error greater than 5 per cent. The results thus far secured have demonstrated the dependability of the methods here given. Scapular types are common to ancient and modern man, and they are inherited variations of unusual constancy; hence they are dependable bases for correlations in routine clinical examinations and in comparative studies of individuals, of families and of various stocks and races. The definite relation of scapular types to the problems of human heredity, longevity, morbidity and adaptability justify the conviction that continued application of scapular classification to these vital and enduring problems will eventually yield rich rewards to the physician and to the race.

THE VALUE OF CLINICAL CARDIODYNAMIC RECORDS *

STEPHEN D'IRSAY, M.D.
SAN FRANCISCO

Methods of functional diagnosis should comply with two requirements: The function to be tested should be precisely known, and quantitative results should be obtained. Neither of these has been exactly fulfilled by the existing methods of functional diagnosis of the heart, first, because the exact nature of the function tested is not given and, second, because the results are not quantitative. In this paper, attention is called to the possibility of elucidating one definite function of the heart by the means of certain graphic methods, phonocardiography and sphygmography. I call these cardiodynamic records. This function, the tonicity, can be considered to depend on the isometric contraction of the myocardium, as expressed in its time element. I will try to bring out some facts in favor of this assumption, after pointing out some well known experimental data on which the hypothesis is based.

THEORETICAL CONSIDERATIONS

Two different forms of contraction occur in all muscle, the isometric and the isotonic. In the first there is no shortening of the individual muscle fibers, but there is a development of internal tension; in the second, actual work is performed, but there is no further increase of the internal tension already developed. In the myocardium, the isometric period of contraction begins with the closure of the atrioventricular valves and ends with the opening of the semilunar valves. From the opening of the semilunar valves until the end of the systole, the muscle acts, on ejecting the blood, by its accumulated tension: this is the isotonic or auxotonic period of contraction, rather auxotonic, because the resistance against which the muscle works gradually increases. The isometric contraction, or isometric period of muscular contraction, is the essential phase of muscular activity from the point of view of energetics.[1] During this isometric contraction, chemical energy of the muscle, partly through the stage of electrical energy, is being transformed into surface energy, creating a state of tension in the fibers.[2] The potential energy of this tension may be transformed into external work. It has been stated that the energy of a contraction is a function of

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1. Hill, A. V.: J. Physiol. **42**:1, 1911.

2. Haber and Klemensiewicz: Ztschr. f. phys. Chemie. **67**:385, 1909.

the area of certain longitudinal surfaces in the fiber:[3] these surfaces are being created or increased during the isometric contraction.[4]

Hill proved this point by showing that the heat produced is proportional to the length of the contracting fibers during the time of contraction, and that the heat developed is greatest during the isometric contraction.[5] Therefore, the work done by the muscle during the isotonic or auxotonic period of contraction depends on this tension, and only after a period of full tension will the work be optimal. This tension is created partly during the isometric contraction and is partly preexisting. The latter element of preexisting tension is commonly called

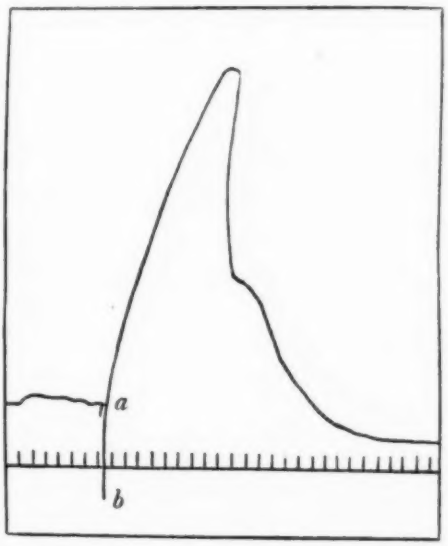

Fig. 1.—The curve demonstrates the ample contraction of smooth muscle on being stretched from *a* to *b*. (From Straub,[6] Fig. 4 B.)

muscular tonus, but I believe that it is identical biologically with the surplus tension built up during the isometric contraction.

Straub[6] and Winkler[7] have shown, on the denervated muscle of Lumbricus and the stomach of the frog, that smooth muscle contracts after stretching (Fig. 1). The isometric contraction of the myocardium is very similar to this, for, with increased venous inflow, the heart is

3. Kozawa: J. Physiol. **49**:233, 1915.
4. Blix: Skandin. Arch. f. Physiol. **5**:150; 173, 1895. Patterson, Piper and Starling: J. Physiol. **48**:465, 1914. Bayliss: Principles of General Physiology, Ed. 3, London, 1920, p. 441.
5. Hill, A. V.: J. Physiol. **47**:305, 1913-1914.
6. Straub: Arch. f. d. ges. Physiol. **79**:379, 1900.
7. Winkler: Arch. f. d. ges. Physiol. **71**:357, 1898.

overloaded and the stretched ventricular muscle performs a greater amount of work, as shown by the increased pressure and volume per beat.[8] It may be said that the law of relation between tension and performance which applies to the skeletal muscle applies also to heart muscle. Gesell,[9] working with the auricle of the tortoise, found that the strength and duration of the total contraction depended on the initial tension.[8] Thus, it can be said that the preexisting tonus of the heart muscle and the tension formed during the isometric period are identical events, from the functional point of view at least.

We may regard another fact as additional proof that the formation of tonus surplus, surface energy or tension is produced during the isometric period of the systole. The initial ventricular complex of the

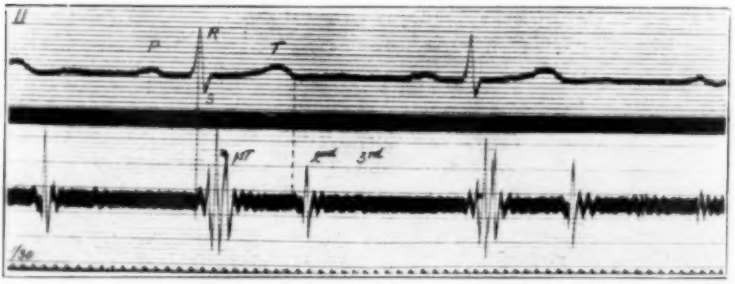

Fig. 2.—Relationship of systole (expressed in phonocardiogram) to electrocardiogram (after Lewis, from Weitz[10]).

electrocardiogram always extends considerably into the isometric period. The systole begins from 0.023 to 0.035 second after the beginning of the ventricular excitation, and always before the S deflection is inscribed or before the R wave ends.[10] Accepting the well established theory of Roaf [11] and others, that the production of acid in the muscle is responsible for both the electrical changes and the changes in the surface tension, and observing that the electrical changes in the ventricular muscle fall in the isometric period of the systole, it may be assumed with great probability that the initiation of the changes in surface tension is, too, in the said period [12] (Fig. 2).

The principal change recorded in the ventricles during the isometric period of the systole is the rise of intraventricular pressure. The curve

8. Straub: Deutsch. Arch. f. klin. Med. **116**:409, 1914. Patterson and Starling: J. Physiol. **48**:357, 1914. Tigerstedt, R.: Physiologie des Kreislaufes, Berlin, **1**, 1921-1923.

9. Gesell: Am. J. Physiol. **39**:239, 1916.

10. Wiggers, C. J.: Electrocardiogram, Arch. Int. Med. **20**:93 (July) 1917.

11. Roaf: J. Physiol. **48**:380, 1914. Mines: Kolloidchem. Beihefte **3**:191, 1912.

12. Mines: J. Physiol. **44**:25, 1912.

recorded by the intraventricular pressure parallels the changes in the internal tension or tonus of the ventricular muscle.[13] It rises suddenly during the isometric period, and maintains itself on a level during the rest of the systole. This harmonizes with the previously expressed view. Hill [14] demonstrated that the oxygen consumption and the developed tension are directly proportional. I have pointed out that the rise in tension and the formed intraventricular pressure are, too, proportional. Since the

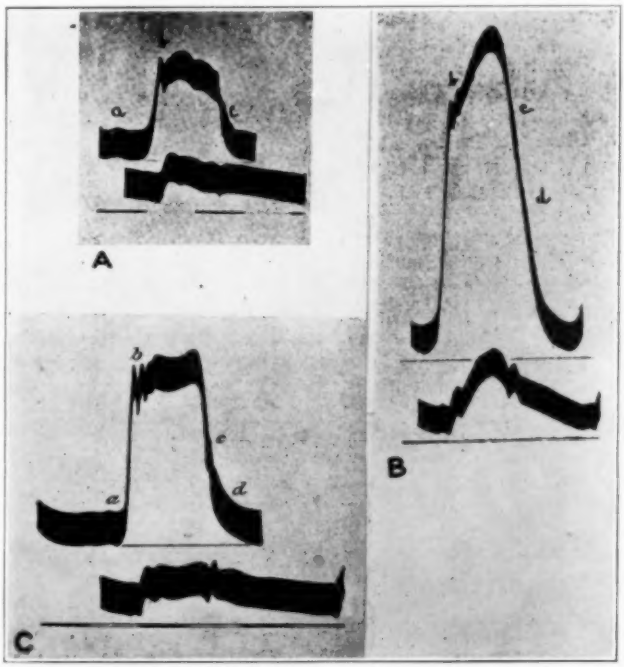

Fig. 3.—Upper, intraventricular pressure, lower, aortic pressure curves from rabbit. *A*, before injection of epinephrin; *B*, immediately after, *C*, after. The curves demonstrate the variance in the steepness of the intraventricular pressure according to the resistance encountered. (From Tigerstedt.[15])

oxygen consumption is a criterion of muscular activity, and this means, considered from the standpoint of energetics, the formation of tonus, then we may conclude that the rise of pressure is the immediate consequence of the tension formed.

The function of the intraventricular pressure is to overcome the aortic pressure, open the semilunar valves and impart kinetic energy to the

13. De Heer: Arch. f. d. ges. Physiol. **148**:1, 1912.
14. Hill, A. V.: J. Physiol. **44**:466, 1912. Bayliss (Footnote 4, third reference).

blood. This means that the promptness with which the semilunar valves are opened depends on two factors: the form and height of the pressure curve itself and the resistance offered to it by the blood pressure in the arterial system. But it has already been pointed out by Frank [15] and confirmingly shown by Tigerstedt [16] that the intraventricular pressure rises in the form of a more or less steep curve, according to the height

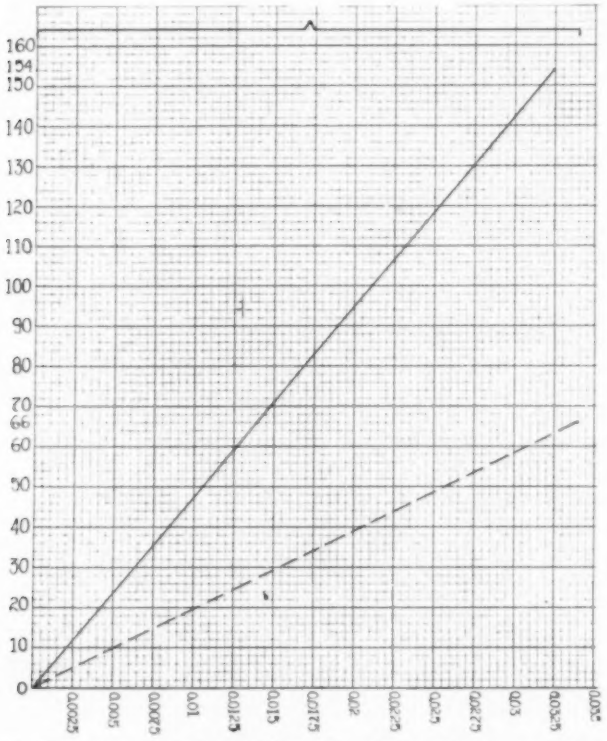

Fig. 4.—The time element is independent of the absolute amount of intraventricular pressure. Abscissa represents time in seconds; ordinate, pressure in millimeters of mercury (constructed after data from Tigerstedt.[16])

which it must attain [17] (Fig. 3). If the total height attained was 154 mm. of mercury, the pressure rose 10 mm. in 0.0024 second, whereas in the case of a total intraventricular pressure of only 68 mm., it rose 10 mm.

15. Frank, O.: Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München **14**:147, 1898.

16. Tigerstedt, C.: Skandin. Arch. f. Physiol. **28**:37, 1912. Tigerstedt, C.: Ibid. **29**:234, 1913.

17. Piper: Arch. f. Anat. u. Physiol. (Physiol. Section), 1912, p. 343; ibid., 1913, pp. 331 and 363; ibid., 1914, p. 365.

in 0.0046 second, showing that under normal conditions the tension of the muscle regulates the pressure necessary to open the semilunar valves within constant time limits (Fig. 4). The constancy of the time element is thus entirely independent of the resistance acting against the intraventricular pressure, in other words, is independent of the blood pressure.[18]

This time limit is given by various authors as varying between 0.02 and 0.1 second.[19] My own values are closer to the lower ones, varying normally between 0.029 and 0.06 second.

I have determined the length of the isometric period by a method similar to that of Wiggers and collaborators.[20] As has been shown, the rise of intraventricular pressure corresponds to the rise of tension in the muscle fibers. The first sound designates the beginning of systole and of the isometric period, and the second sound the end of systole, which corresponds to the incisure of the central sphygmogram preceding the dicrotic wave. If records of the heart sounds and sphygmograms of the carotid are taken simultaneously and the interval between the first and second sounds is marked off on the sphygmogram back from the incisure, the interval during which the atrioventricular and semilunar valves are closed will be obtained. The rise of the primary wave in the carotid artery designates the beginning of the outflow of blood with the deduction of the average between 0.007 and 0.017 second, this being the time the blood requires to flow from the semilunar valves to the receiving region in the carotid artery.[21] The oscillations of this factor however do not exceed 10 per cent. (plus or minus) of the length of the isometric period and 1.5 per cent. of the total systole, and

18. Weitz and Grauer: Deutsch. Arch. f. klin. Med. **116**:512, 1914. Lüderitz: Ztschr. f. klin. Med. **20**:374, 1892.

19. Chauveau and Marcy: Mém. Acad. de med. **26**:282, 1863. De Heer (Footnote 13). Edgren: Skandin. Arch. f. Physiol. **1**:67, 1889. Einthoven and Geluk: Arch. f. d. ges. Physiol. **57**:617, 1894. Grunmach: Virchows Arch. f. path. Anat. **102**:565, 1885. Hess: Ergebn. d. inn. Med. u. Kinderh. **14**:359, 1915. Hochhaus: Arch. f. exper. Path. u. Pharmakol. **31**:405, 1893. Hürthle: Arch. f. d. ges. Physiol. **49**:29, 1891. Keyt: Sphygmography and Cardiography, New York, 1887. Landois: Die Lehre vom Arterienpuls, Berlin, 1872. Marey: La circulation du sang, Paris, 1881. Müller and Breuer: Deutsch. Arch. f. klin. Med. **104**:119, 1911. Pezzi: J. de physiol. et de path. gén. **15**:1178, 1913. Piper (Footnote 17, first reference). Rivé: De Sphymograaf en de sphymographische Kurve, Utrecht, 1866. Robinson and Draper: Deutch. Arch. f. klin. Med. **100**:347, 1910. Schmidt: Ztschr. f. klin. Med. **22**:393, 1893. Swann, A. W., and Janvrin, E. R. P.: Arch. Int. Med. **12**:117 (Aug.) 1913. Tigerstedt (Footnote 8, third reference); Skandin. Arch. f. Physiol. **20**:249, 1908; (Footnote 16, second reference). Weitz and Grauer (Footnote 18, first reference). Weitz: Ergebn. d. inn. Med. u. Kinderh. **22**:402, 1922. Wiggers, C. J., and Clough, H. D.: J. Lab. & Clin. Med. **4**:624 (July) 1919.

20. Wiggers, C. J., and Clough, H. D.: J. Lab. & Clin. Med. **4**:624 (July) 1919. Wiggers, C. J., and Dean, A. L., Jr.: Am. J. M. Sc. **153**:666 (May) 1917. Wiggers, C. J.: Cardiac Murmurs, Arch. Int. Med. **22**:28 (July) 1918.

21. Robinson and Draper: Deutsch. Arch. f. klin. Med. **100**:347, 1910.

are able to influence our results in only a correspondingly slight degree (Fig. 5).

Wiggers and Clough [22] showed that the isometric period is apt to be prolonged in disease,[23] but Weitz [24] and others [25] deny this, and maintain that the isometric period is independent of any other value, including the aortic pressure. It is the percental relation between the fixed time interval of the systole and the (physiologically) equally fixed time interval of the isometric period that must be considered. In the isometric contraction, three factors are cooperating, the intraventricular pressure depending on the ventricular tonus, the arterial pressure antagonizing it and the time factor. The time being constant under given conditions,

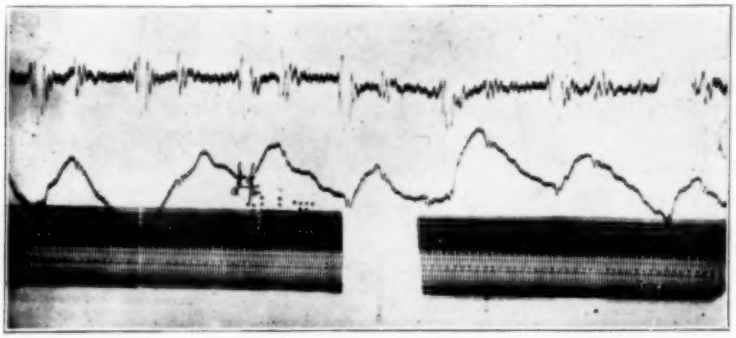

Fig. 5.—Phonocardiogram and carotid sphygmogram; *a-b*, isometric period of systole; time marked, 0.01 second.

it is the tonus that must adapt itself. Normally, this is done, but if the level of the initial tonus is low, or if the increase in tension during the isometric period is feeble, the time factor must lose its rigidity in order to enable the intraventricular pressure to overcome the aortic or pulmonic pressure and open the semilunar valves. Thus, the isometric period will be prolonged and its percental relation to the total systole will increase. The average value for the length of the isometric period, as determined from dynamic records, is 16.72 per cent. of the entire systole. Changes in the rate alone cause hardly any variation in this percental relation.

ANALYSIS OF RECORDS

One hundred cases have been analyzed by the graphic methods discussed above. They have been divided into four groups, quite

22. Wiggers and Clough (Footnote 19, first reference).
23. Robinson (Footnote 21). Müller and Breuer: Deutsch. Arch. f. klin. Med. **104**:119, 1911. Pezzi (Footnote 19, thirteenth reference).
24. Weitz: Ergebn. d. inn. Med. u. Kinderh. **22**:402, 1922.
25. Hess: Ergebn. d. inn. Med. u. Kinderh. **14**:359, 1915.

arbitrarily, with no clinical or pathologic preconceptions, but solely on the basis of the percental relation between the duration of the isometric period and that of the systole. In the first group have been classified cases the isometric period of which constituted less than 10 per cent. of the length of the total systole; to the second belonged cases in which it was from 10 to 15 per cent.; in the third group, the values lay between 15 and 20 per cent., and in the fourth group we listed those in which the isometric period was more than 20 per cent. of the total systole. Ten per cent. of the total material belonged to the first, 28 per cent. to the second, 35 per cent. to the third, and 27 per cent. to the fourth group. Considering the clinical phenomena, we find diverging results in each one of these groups, and it is the last one that shows the most marked differences.

In the first group (ten cases), five were individuals under the age of 17—three of them young children—and the remaining five were under 30. In only three were there clinical symptoms of heart disease. In three of the group, the electrocardiogram showed left ventricular preponderance (in a slight degree, none exceeding an electrical axis of —6 degrees), in one of which this preponderance was attributed to a mild arborization block. None of the members of Group 1 showed clinical signs of decompensation. It seems that values below 10 per cent. are frequent in childhood and are not associated with loss of tonicity.

The second group (twenty-eight cases) comprised patients with ages varying from 9 to 54 years. Myocardial disease was demonstrable in three, one showing complete atrioventricular dissociation and two auricular fibrillation, with alterations of the direction of T in more than one lead. Clinically, eight had chronic valvular disease; three were cases of irritable heart (with respiratory arrhythmia and marked cyclic alterations of the electrical axis); four were cases of hyperthyroidism with cardiac symptoms; two others were at the last cases of congenital valvular disease, while eight had no clinical signs of heart affection. All the patients with valvular disease were well compensated. One of the patients with auricular fibrillation (of arteriosclerotic origin) showed symptoms of incipient heart failure, whereas the patient with atrioventricular dissociation was seriously decompensated, with pleural effusion and high values of venous oxygen unsaturation. The electrocardiographic findings of this group included signs of increased auricular activity in three cases, and two mild left ventricular preponderances. Only three, 6 per cent. of this group, showed serious myocardial disorder and fifty-three, 58 per cent., had no organic heart lesion.

In the third group (thirty-five cases), six patients showed definite signs of myocardial disease; viz., three, angina pectoris; one, acute myocarditis; one, arteriosclerotic auricular fibrillation, and one, who

exhibited electrocardiographic evidences of disturbed intraventricular conductivity, together with ventricular extrasystoles arising in multiple foci, was accordingly in a state of potential ventricular fibrillation. This constitutes seventeen cases, 14 per cent. of the entire group. The fact must be emphasized that, of these six cases, three showed percental values of the isometric period at or beyond the range of normal; namely, 19.93 per cent., 18.46 per cent. and 19.69 per cent. These border on the next or pathologic group. Among cases without electrocardiographic evidence of myocardial disease, we find two patients with cardiorenal sclerosis, one of whom showed a percental value for the isometric period of 19.04 per cent., which again borders on the pathologic. There were ten patients with valvular disease: one, who had mitral stenosis, disclosed signs of clinical decompensation and had 19.34 per cent. as the relative value of the isometric period. There was one case of congenital valvular lesion, four cases of irritable heart and one case of hyperthyroidism. The other patients, eleven, evidenced no signs or symptoms of cardiac disease; thus, only 45.41 per cent. of this group, the minority of patients, were free from organic heart affection. This percentage, however, would increase with the shifting of the five cases with isometric period values approximating 20 per cent. to Group 4.

Group 4 comprises cases exhibiting percental values of the isometric period above 20 per cent. In the twenty-seven cases of this group, ten showed definite signs of severe myocardial disease, some with auricular fibrillation developed on an arteriosclerotic or infectious basis, some with well marked symptoms of angina pectoris. We can add to these ten two cases of cardiorenal sclerosis evincing signs of cardiac decompensation, eight cases of chronic endocarditis, three of which were in the stage of heart failure (two being mitral stenosis and one aortic insufficiency); furthermore, one case of congenital heart disease. Thus, twenty-one members of Group 4 (comprising twenty-seven) had definite organic lesions, most of them with signs of cardiac failure. In the remaining six, too, we found many phenomena of cardiac disease, although it was not possible to demonstrate well defined organic lesions. In two there was to be found advanced pulmonary emphysema with strong preponderance of the left ventricle (the electrical axis being between — 6 and — 35 degrees). In two others, an abnormal auricular activity was encountered, evidenced by ectopic auricular rhythm and frequent auricular extrasystoles, together with marked left ventricular preponderance.

The sixth deserves to be mentioned separately. This was a case of Addison's disease.

The findings are summarized: The age was 14; the blood pressure was 85 systolic, 60 diastolic; there was an inverted T_2 and T_3 in the

electrocardiogram, the electrical axis being 79 degrees; the teleroentgenogram showed a perpendicular heart (Fig. 6), the isometric period being 23.5 per cent.

These data, taken separately, are indefinite in their meaning, but they harmonize in giving a picture of myocardial hypotonicity, corresponding to the high value of the isometric period. Thus, an involvement of the heart is present in 96.3 per cent. of the group, only one case being found to be free from any lesion of the circulatory system. Group 4 is sharply set off from the others, particularly from Groups 1 and 2; Group 4 shows the parallel development of the prolongation of the

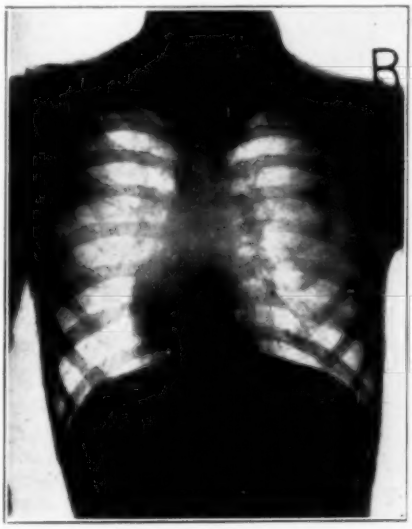

Fig. 6.—Perpendicular heart in case of Addison's disease, associated with myocardial hypotonicity.

isometric period and definite cardiac disease, particularly of arteriosclerotic origin. The accompanying table summarizes the results.

Summary of Data

Group	No. of Cases	Relative Length of Isometric Period, Per Cent.	Cases with Clinical Cardiac Disease, Pr. Ct.	Age
1	10	<10	33.3	From 2 to 29 years
2	28	10-15	46.4	From 9 to 54 years
3	35	15-20	54.6	From 15 to 65 years
4	27	>20	96.3	From 14 to 62 years

Shifting the five cases with isometric period values approximating 20 per cent. from Group 3 to Group 4, we obtain in Column 4 for Group 3, 46.7 per cent., bringing it down to the level of Group 2, whereas for Group 4 we get 96.9 per cent.

SUMMARY

1. It is known that the period of muscular contraction, both cross-striated and cardiac, during which the internal tension reaches the degree necessary for the performance of external work is the isometric period.

2. The isometric contraction of the myocardium is performed during a given, fixed period of time and is counterbalanced by a given, fixed resistance.

3. On this basis, consideration has been given to the idea that in myocardial diseases that involve a decrease in myocardial tonus, the duration of the isometric period in its relation to the duration of the total systole might be disproportionately prolonged.

4. The percental relation of the isometric period to the total systole can be regarded as the function of tonicity.

5. Its normal value is from 15 to 16 per cent., but there seems to be no definite lower limit. However, the value rarely goes under 13 per cent.

6. The upper limit can be set down at 18 per cent. Values above that ought to be considered pathologic.

7. The highest values are mostly shown by cases of cardiorenal sclerosis.

8. It might be possible in the functional diagnosis of the heart to use the foregoing method which aims at the elucidation of one function, that of tonicity.

SKIN CAPILLARIES IN SCLERODERMA*

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Visual exploration of the skin capillaries by the Lombard [1] method has revealed, in certain diseases, changes in form, size, tonus, flow and reactions to certain stimuli. The study of the skin capillaries in the dermatoses has been reported by Niekau,[2] Michael [3] and others, in which they have noted certain changes in form and function of these vessels. There is as yet no standard established for capillary morphology in normal persons. Sufficient observations have been reported, however, to distinguish definitely from the normal some of the morphologic, numerical and functional variations in the capillaries observed in certain types of cardiovascular-renal disease, polycythemia, Raynaud's disease and related vasomotor states, shock, and a few of the dermatoses. Many of the variations in morphology are only slight. Changes affecting size and number of functioning capillaries, as pointed out by Krogh,[4] are of greater importance. Pathologic classification should be based on quantitative comparative studies with a large control group in normal persons, and with due consideration of age. These studies should include capillary morphology, size, incidence of tortuosity, flow rates and abnormal types of flow. In this manner, comparisons could be made which would undoubtedly throw additional light on the disturbances of vascular physiology in many different diseases.

The capillary variations observed in cases of primary diffuse scleroderma are striking, but it would not seem justifiable to believe that the capillary changes precede the pathologic hypertrophy of the connective tissue bundles. However, it would appear that a close relationship probably exists between these abnormal vessels and the pathologic changes of the skin. In borderline or vasomotor scleroderma, the capillary studies reveal changes in form and behavior similar to those observed in Raynaud's disease, suggesting that the vascular disturbance

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1. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, Am. J. Physiol. **29**:335-362, 1911-1912.

2. Niekau, Bruno: Anatomische und klinische Beobachtungen mit dem Hautkapillarmikroskop, Deutsch. Arch. f. klin. Med. **132**:301-334 (July) 1920.

3. Michael, J. C.: Dermatoscopy; A Study of the Blood Vessel Form and Arrangement in Various Dermatoses, Arch. Dermat. & Syph. **8**:603-618 (Nov.) 1923.

4. Krogh, August: The Anatomy and Physiology of the Capillaries, New Haven, Conn., Yale University Press, 1922.

precedes and stands in direct causal relationship to the secondary change in the skin.

Cases presenting skin changes of scleroderma may be divided into three groups: (1) the diffuse, primary, progressive scleroderma, (2) borderline, or secondary vasomotor, types, and (3) the localized form, or morphea, which was not included in this study. In this report are included five cases of the diffuse primary scleroderma type, Group 1 (Table 1), and five of the borderline, or vasomotor, type, Group 2 (Table 2). The cases in Group 1 present varying degrees of hide binding, and reduced capillary function. Trophic ulcerations were

Fig. 1.—Appearance of hands in Case 5; true sclerodactylia.

observed in four cases; sclerodactylia in two (Fig. 1). Color changes preceded or accompanied the lesions of the skin. They were mild, usually presenting only one phase; in two cases, there was early pallor of the hand, and in two, a mild cyanosis, and in one of these associated facial rubor. In one case, there were no color changes. In Case 5, the earliest symptom was peripheral asphyxia of the hands, aggravated by cold. Syncope or pallor was not observed. Excessive susceptibility to cold, before the recognizable onset of the condition, existed in one instance only, but cold as an exciting or aggravating agent was present in all but Case 3. The hands were affected first, in all cases; the areas were multiple, in five cases. The affected peripheral areas were cold

TABLE 1.—*Observations on the Capillaries in Diffuse Primary Scleroderma*

Case	Description	Age and Sex*	Blood Pressure: Systolic	Blood Pressure: Diastolic	Loops Each Millimeter	Total Length of Visible Capillaries, Mm.†	Caliber of Limb, Mm.: Arterial	Caliber of Limb, Mm.: Venous	Capillary Flow, Millimeter Each Second‡	Observations of Flow	Description of Capillaries of the Nail-Fold
1	Diffuse lesion, mostly on hands and face	50 ♂	Right arm 92	64	4	0.58 0.78	....	....	0.30 0.15	Slow, uniform flow in all capillaries; no stasis; cells apparently crowding into venous limb	Huge, giant capillaries; dilatation of venous limbs, less marked in arterial limb
			Left arm 110	70		0.76 0.49	....	....	0.15 0.30		
2	Diffuse lesion, most marked in hands; small trophic ulcers on tips of fingers; sclerodactylia	31 ♂	100	74	2-3	....	....	....	0.01 Difficult to distinguish flow	Capillary stream slow; uniform in all loops; segmented appearance of stream; movement not perceptible in many loops; trace of cyanosis in capillary blood	Huge, dilated or giant types of capillaries; few small, thin loops; tortuosity in 50 per cent. of the loops
3	Well defined lesions on hands and face	47 ♂	110	70	2-3	0.43	.....	....	Movement of stream obscured by changes in skin	Difficult to determine movement of stream; skin obscured by trophic changes	Many loops appear as thrombosed areas, size not determined; occasional giant type
4	Marked diffuse boardlike lesions on hands and face	37 ♂	120	60	4	0.46 0.50	0.096	0.128	Movement of stream obscured by indurated skin	Obscurity of skin masks movements of capillary flow; few loops show cyanosis	Long, dilated, feathery looking loops; few shapeless thrombosed areas
5	Marked boardlike induration on hands, arms and face; sclerodactylia	27 ♀	115	65	3	0.66	0.128	0.016	0.1 0.1 0.014 0.08 0.07	Flow very slow and granular; some intermittence with periods of stasis; no flow disturbance with exposure to cold	Large giant type of loops, averaging three to a field; some obscurity of capillary outline

* In this and the following table, ♂ indicates male, ♀ female

† The visible capillary loop is measured; the transition point from capillary to venule and artery is not always clearly defined.

‡ Room temperature, 24 degrees.

to touch; this was independent of color. Difficulties of flexion were present in all cases. The molded mask-like expression of the face and restricted ability to open the mouth were noted in three cases.

In the cases in Group 2, the earliest symptoms suggested the abnormal vasomotor reactions observed in Raynaud's disease. In Case 6, the stiffening of the skin was noticed two years after the appearance of the peripheral syncope. The sclerodermatous changes were moderate, and the hands had a swollen appearance, extending up as far as the elbow, but the definite induration observed in Group 1 was absent. Susceptibility to cold with mild peripheral color changes had been present in varying degrees for a number of years. The skin, in four cases in this group, was firm, smooth and unyielding, but not typical of the skin in cases of true scleroderma; changes were noted only in parts presenting the vasomotor phenomena. Minor difficulties in flexion of the hands were present in three cases. Similar involvement in the skin of the feet existed in Case 6. The dystrophic alteration of the skin was more or less transitory, in the cases in this group. A seasonal variation was observed, cold always precipitating or aggravating the condition, and increasing the difficulty of swelling and flexion. There was localized hyperhidrosis in this group, which interfered slightly with accurate visualization of the loops. These cases exhibited, in varying degrees, the well defined color reactions of Raynaud's disease. Pain was a minor feature. The attacks were not clearly defined, and the subjective symptoms were mild, usually of a burning or tingling character.

METHODS OF STUDY

A stereomicroscope was used with magnifications of 60 and 120 diameters. A special ribbon filament light, with condensing lens and suitable heat and color filters, was devised to minimize the effect of heat and color rays on the capillaries. A stabilizer for the fingers, consisting of a small iron trough with rubber buffers, gave sufficient immobilization to assure fairly accurate quantitative studies. Eye piece micrometers with divisions of 0.01 and 0.0025 mm. were employed with the low and high magnifications. Photomicrographs were made in several instances, but the difficulties in securing short exposures and mobilization of the part had not been surmounted sufficiently early to allow its routine use in every case.[5] All fingers were examined, and representative areas selected for study. As changes above or below room temperature exert a marked effect on capillary flow, a fairly uniform room temperature was maintained at from 24 to 26 degrees C.

5. Dr. Sheard of the section on physics has recently perfected a method for obtaining photographs of skin capillaries by reflected light in from 1/10 to 1/50 second exposures.

TABLE 2.—*Observations on the Capillaries in Raynaud's Disease Associated with Sclerodermal Changes in the Skin*

Case	Description	Age and Sex	Blood Pressure		Loops Each Millimeter	Total Length of Visible Capillaries, Mm.	Caliber of Limb, Mm.		Capillary Flow, Mm. Each Second	Observations of Flow	Description of Capillaries
			Systolic	Diastolic			Arterial	Venous			
6	Mild diffuse lesions of the hands and feet; vasomotor disturbances; trophic thickening of index finger	60 ♀	178	84	7	0.50	.....	.....	0.15 0.16	Variation in flow; few loops, slow flow; stasis in others in from two to ten minutes; marked slowing response to cold with cyanosis	Ragged dilated loops; few thrombosed areas; several large types; normal number for each field
7	Mild diffuse scleroderma-tous changes; definite Raynaud's syndrome in hands and feet	26 ♀	104	80	6	0.54	0.08	0.08	0.15 0.20 0.01 0.03 0.06 0.03	Slow regular flow; few loops show complete stasis; cold produces marked slowing in all loops with stasis; many plasma spaces	Broad dilated loop; no giant forms; capillary picture that of Raynaud's disease rather than scleroderma; normal number for each field
8	Waxy, diffuse, firm swelling of hands and feet; color changes suggesting Raynaud's disease	37 ♀	100	74	6	0.44	.....	.....	0.20 0.14 0.12 0.22 0.05 0.07 0.05 0.07	Flow extremely slow; fairly uniform; greatest delay in venous limb	Broad, dilated loops; bizarre shapes; occasional giant type of loop seen; normal number for each field
9	Nonfilling, swelling of arms, hands and feet; pale and cold to touch; flexion difficulties; trophic area, first finger, right hand	29 ♂	...	...	4	0.26	0.08	0.036	0.09 0.05 1.1 0.05	Flow difficult to see; slow, not uniform; stasis observed	Loops rather broad; hazy appearance; usual, thick, hairpin pattern; decreased number of loops
10	Skin of hands was firm, thickened; some flexion difficulty; pale, cyanotic, cold; trophic ulceration, tips of fingers	26 ♀	140	100	5	0.65	..... 0.056	0.048 0.128	0.15 0.10 0.12 0.08 0.07 0.06	Intermittent fast and slow flow; plasma spaces and periods of stasis; rocking flow observed; marked stasis reaction to cold	Many huge dilated loops; diminished number in field; few normal-sized loops

NORMAL CAPILLARIES

Morphology (Fig. 2).—The nail-fold capillaries have been fairly well studied in normal subjects. In subjects under the fifth decade of life, the predominant type of loop is the straight or hairpin pattern, with a small incidence of tortuosity. The percentage of tortuous loops helps to decide the question of normality, since their number increases with age. Tortuosity per se is not of value unless the age of the subject is considered. The decision of the existence of a pathologic condition cannot be made by the capillary morphology unless these changes are definite. Local trauma can disturb the arrangement of the nail-fold

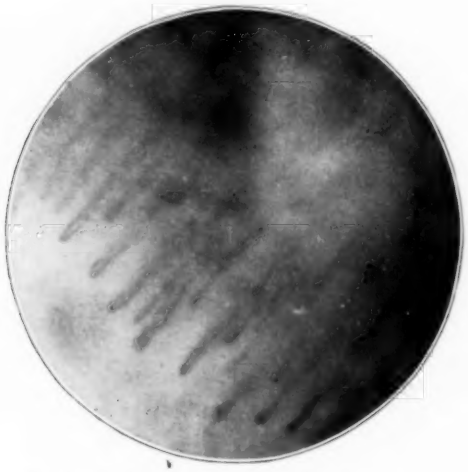

Fig. 2.—Normal nail-fold capillary (×60).

capillaries. This is observed as the result of excessive manicuring. Single loops may show marked abnormalities in normal subjects.

Size.—The total length of the visible capillary loops has been determined in a group of normal subjects in the different decades of life, and was found to average 0.42 mm. The venous limb is slightly longer and wider than the arterial, the caliber averaging 0.014 mm. The caliber of the arterial limb averages 0.011 mm. The average number of loops for each linear millimeter varies from 7 to 12.[6]

Capillary Flow.—The flow is usually fast and fairly uniform. In occasional loops, the stream may be broken or segmented, or, at times,

6. In our previous paper, The Skin Capillaries in Raynaud's Disease (Arch. Int. Med. **35**:56 [Jan.] 1925), the values of the normal calibers in the nail-fold capillaries were too low. Recalculations by means of the photographic and enlargement method have given the values in this paper.

there may be complete disappearance of a loop. The rate of flow varies with age. In the fourth and earlier decades, the majority of loops have flow rates in excess of 1.5 mm. each second, and cannot be measured with accuracy. In later decades, a definite slowing of capillary flow has been demonstrated in individuals with normal range of blood pressure. Temperature modifies the capillary flow markedly.

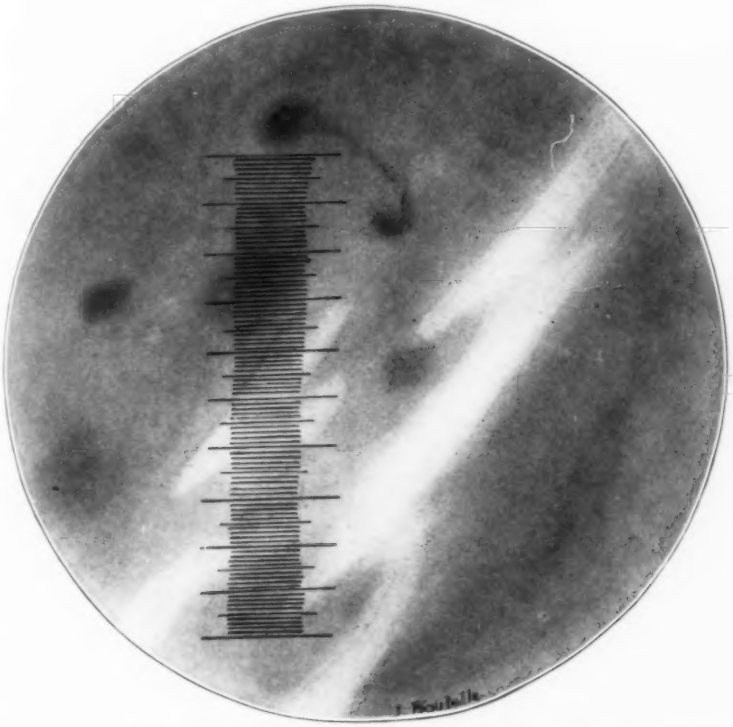

Fig. 3.—Nail-fold capillaries in case of primary scleroderma, showing marked sparsity of loops and thrombosed appearance; complete loss of normal capillary morphology (artist's sketch drawn to scale; smallest division 0.01 mm.).

These estimations were determined under fairly constant conditions with room temperature ranging from 24 to 26 degrees.

Capillary Tonus.—The degree of capillary tonus is evidenced by contraction or dilatation in the arterial and venous limbs. Müller [7] designates contractile changes in the capillaries as spasm and stasis in the

7. Müller, L. R.: Studien über den Dermagraphismus und dessen diagnostische Bedeutung, Deutsch. Ztschr. f. Nervenh. **47-48**:413-434, 1913.

precapillary and postcapillary vessels. In the normal capillaries, these phenomena are rarely seen under control conditions, and then only in isolated loops. In the mild types of acrocyanosis in the asthenic type of person, dilated atonic capillaries are observed. In later decades of life, increased tonus is the rule.

Capillary Permeability.—Direct evidence of disturbances in capillary permeability are occasionally observed, in which free hemoglobin pig-

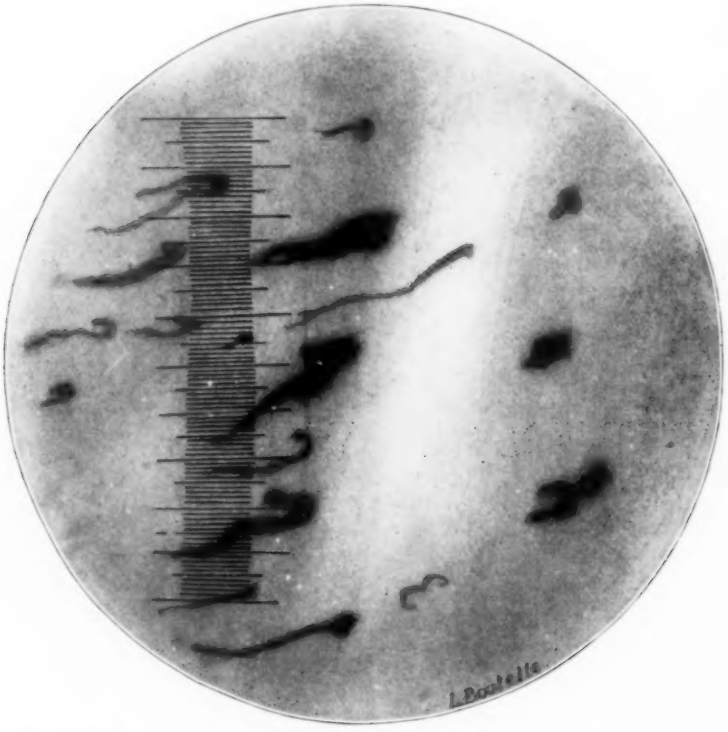

Fig. 4 (Case 4).—Loss of normal morphology; huge, dilated and sparse loops (scale same as in Figure 3).

ment is seen distal to the loop with intact capillaries. We have observed this, in several instances, in cases of acute glomerular nephritis and in two apparently normal persons, in whom trauma was apparently not a causative factor, since present only in isolated vessels. The minor degrees of puffiness of the hands associated with mild rubor or cyanosis and hyperhidrosis are probably related to disturbances in capillary permeability.

OBSERVATIONS ON THE CAPILLARIES IN CASES OF PRIMARY SCLERODERMA

Group 1 (Table 1).—The most striking finding in the skin capillaries, in the cases of true scleroderma, was the presence of huge loops or so-called giant capillaries (Figs. 3 and 4). The total length of the larger loops was found to range from 0.5 to 0.8 mm. The total number of loops for each linear millimeter averaged 3.5, which is one-third the number observed in normal subjects. Frequently, only one or two large capillaries were seen in a field. This decreased incidence of loops seemed to stand in direct relationship to the degree of trophic disturbance. The diameter of the venous and arterial limbs was much greater than that of normal vessels. Often a loop was so greatly enlarged that the space between the two limbs was obliterated, giving the capillary the appearance of a large, red, vaguely defined area. These abnormalities were permanent, and transitory changes in the caliber of the loops, as the result of temperature changes and mechanical irritation, were not observed. The capillary outline was usually frayed and indistinct, giving the loops a feathery appearance. This was due to the decreased visibility of the skin as a result of its collagenous hyperplasia. All the capillaries did not exhibit the same degree of morphologic changes. Occasional loops appeared normal. The venous limb was slightly dilated in most of the loops, and was always less marked than the arterial segment.

Capillary Flow.—The capillary flow, in this group, was extremely difficult to study. The changes in the skin did not allow visualization of the leukocytes, thus making measurements of flow impossible, in most instances. The movement of the blood, in the giant loops, was slow, and fairly uniform in different loops. Short periods of stasis were observed in Case 5, but marked cyanosis of the capillary blood was not present at room temperature. Stasis was not observed in any degree approaching that observed in the vasomotor cases. Agglutination phenomena and plasma gaps were not present. The blood flow in the capillaries was fast enough to maintain a red color of the cells, that is, a rate exceeding 0.1 mm. each second.

CAPILLARIES IN VASOMOTOR GROUPS WITH SCLERODERMA

Morphology (Table 2).—In the vasomotor type of case, the capillaries present an entirely different picture which may be useful in differentiating the confused clinical complexes which are now roughly classified as scleroderma. The essential difference is shown by the capillaries which resemble in form, size, tonus, function and behavior those observed in true Raynaud's disease. Permanent obliteration of the loops is rare. The average number of capillaries for each linear

millimeter was six. The large giant loops were observed in only four cases, but the usual capillary pattern was preserved, and the large shapeless loops observed in cases of true scleroderma were not simulated (Fig. 5). Decreased tonus with dilated arterial or venous segments was evident, and was heightened by cold. Many loops had the feathery or frayed appearance due to the impaired transparency of the skin, although this was much less than in cases in Group 1. The length of

Fig. 5 (Case 7).—Raynaud's disease with sclerodermal changes; segmented stream and plasma gaps in many loops. Three dilated loops are visible, but do not approach in size those observed in primary scleroderma; several loops show stasis.

the visible loops was 0.48 mm., which is slightly longer than the average normal visible loop. The caliber of the venous and arterial limb in one case was 0.096 and 0.08 mm., respectively. The incidence of tortuosity was not increased by age.

Capillary Flow.—The flow was inert, in many loops, at room temperature. The stasis period varied from a few seconds to several

minutes. There was no uniformity of stasis, since contiguous loops exhibited stasis, slow flow or fairly rapid flow; the latter was the rarest. Cyanosis was present in the static loops. When the capillary flow was less than 0.1 mm. each second, cyanosis was recognizable; this point has been designated as the capillary cyanosis threshold. The flow was usually segmented, with plasma gaps, and other characteristics observed in true Raynaud's disease.[8] In several instances, the reactions to cold were quite similar to those in Raynaud's disease. The behavior of single loops was studied in the different color phases in one case. In the pallor or syncope phase, contracted, partially filled loops were present; many loops were invisible. In the asphyxia phase, clumps of cells

Fig. 6 (Case 10).—Capillary in case of Raynaud's disease and secondary scleroderma. Only three loops are shown: one at right, contracted, one at left, normal, and one dilated loop. The flow was inert in all loops (×60).

were seen to enter the loops slowly from the arterial and venous sides; then complete stasis, increasing cyanosis and dilatation of the loops developed. The rubor phase occurs when the flow is resumed with the blood changing to bright red, due to the presence of oxyhemoglobin. This stage is often incomplete and, in many loops, there will still be varying degrees of stasis, or alternating periods of fast and inert flow (Fig. 6).

COMMENT

The clinical differentiation of certain phases of scleroderma, Raynaud's disease and acrodermatitis chronica atrophicans is still somewhat

8. Brown, G. E.: The Skin Capillaries in Raynaud's Disease, Arch. Int. Med. **35**:56 (Jan.) 1925.

confused. Frequently, vasomotor phenomena, such as cyanosis or mild degrees of peripheral syncope, precede or coexist with the early changes in scleroderma. In the cases presenting the picture of primary or true scleroderma, the vasomotor symptoms are inclined to be mild, presenting only one color phase, unassociated with pain, and not presenting the color responses to cold so characteristic of true Raynaud's disease. This clinical observation is likewise borne out by observations on the capillaries. The numerical decrease in capillary loops was constant in the five cases of Group 1, in contrast to the borderline or vasomotor type of cases in which a fairly normal number of loops were observed. In every case of Group 1, large hypertrophied or so-called giant types were present. The cause of these large vessels might be explained in one of two ways: they may represent a simple capillary hypertrophy, compensating for the decreased number of loops, or they may be a pathologic state related to the fibrotic changes in the corium, that is, back pressure effects. The latter explanation seems more plausible. From the data which we have obtained, we are unable to determine whether the capillaries are a primary or secondary cause of the changes in the skin. The gradual increase in waxy appearance and trophic mutilations accompanying the progression of the disease is associated with single phase color changes, thus indicating capillary impairment. The skin may appear dead and waxlike, or mottled and marmorated. In the more chronic cases, a diffuse pigmentation occurs. The pallor, representing vascular deficiency, is due to a gradual obliteration of many of the capillaries and postcapillary venules. The coldness of the affected portion attests to diminished arterial flow. These vascular changes seem to parallel rather than precede the changes in the skin. It also was observed that the more advanced the sclerodermatous process, the more marked was the capillary deficiency and the incidence of the giant loops. The impaired blood supply of the skin is visualized by the capillary picture, and explains the incidence of trophic lesions in the primary or true type of scleroderma.

The observations on the capillary flow in cases of Group 1 seem to make more definite the distinctions between the primary and borderline or vasomotor types of scleroderma. In the former group, a fairly uniform, slow movement of the cells was observed. Stasis was rare and, when present, was moderate. No intermittent flow, plasma gaps or agglutination phenomena were observed. A crowding of the cells into the venous limb suggested an obstruction in the postcapillary venule. The flow was not slow enough, that is, below 0.1 mm. each second, to produce definite cyanosis. In the vasomotor group, the morphologic changes in the capillaries were slight, but disturbances of flow were marked. Many of the loops exhibited complete stasis, or alternating

periods of flow and stasis. The flow varied markedly in contiguous loops. Plasma gaps and agglutination processes were common. Cyanosis was present in many of the loops in the compensated stage. The capillary reactions were studied in the different color phases in Case 7. In the syncope phase, there was contraction of capillaries, arterioles and probably venules. In the asphyxia phase, clumps of cells were seen to enter the capillary loops from both the arterioles and venules, indicating incomplete relaxation of these vessels. The capillary flow was inert, and cyanosis increased with increasing dilatation of the loop. After variable periods of time, the flow was resumed with bright red, oxygenated blood. The capillaries thus presented an entirely different picture in the two types of cases. In Group 1 vasomotor phenomena are slight or absent, while in Group 2 these phenomena predominate in the capillary picture. The trophic disturbances, in Group 1, are probably related to quantitative capillary deficiency, whereas, in the vasomotor cases, these disturbances are due to capillary stasis and starvation of tissue, which explains the constancy of manifestations in the skin in primary cases, and the more transitory phenomena in vasomotor cases.

The relationship of the capillary behavior and the disturbances of the skin observed in the vasomotor cases can be explained on the basis of Krogh's experimental work. He found that, when urethan was applied to the capillaries of the tongue of a frog, a marked dilatation occurred with ocular evidence of increased capillary permeability. The cells clumped together with loss of plasma and stasis. Thus, capillary dilatation and stasis represent increased capillary permeability. We could believe that the disturbance in permeability in the vasomotor group, as evidenced by the length of stasis and agglutination phenomena, is sufficient to produce an upset in the tissue-blood equilibrium, involving disturbance of the hydrostatic and osmotic pressures with loss to the capillary blood of water and possibly of colloids. The transitory swelling or puffiness of the skin is clinical evidence of this disturbed equilibrium. We believe that the vasomotor group comprises cases of Raynaud's disease in which the phenomena of water-colloid disturbance has reached a degree to cause changes in the water content of the skin, simulating those of scleroderma. Practically all cases of Raynaud's disease reveal some evidence of metabolic disturbance of the skin. This may be represented merely by excessive localized sweating, cold, or by minor degrees of puffiness or swelling. When these alterations exist in sufficient degree, simulation of true scleroderma occurs.

The histopathologic picture of the clinically recognizable scleroderma is that of an increase in connective tissue elements in the corium and subcutaneous tissue, with a diminution in the caliber of the vessels, and thickening of the media and the adventitia, proceeding to atrophy from

the scleroses, and pressure. However, in the early cases of scleroderma in which the foregoing processes have not as yet occurred, the value of a biopsy becomes limited. The use of histopathologic study in the Raynaud syndrome does not, as a rule, permit of definite deductions. Therefore, the taking of a biopsy in these borderline cases will not help materially in the differentiation.

Although a successful treatment is not available in either group of cases, the differentiation of these types is of more than academic interest, since the pathologic basis for a rational treatment would differ diametrically in both groups.

SUMMARY

The nail-fold skin capillaries were studied quantitatively in a series of ten cases, five of which presented a definite picture of scleroderma, and the remaining five essentially a Raynaud syndrome with associated sclerodermatous changes. From the difference in capillary morphology, size, tonus and flow, the cases were divided into two groups: Group 1, true diffuse scleroderma, in which there was a quantitative deficiency of capillary loops, which roughly paralleled the trophic disturbances, and Group 2, the borderline or vasomotor type, in which the skin disturbances were apparently secondary to the abnormal vasomotor reactions, with dilatation, stasis and permeability disturbances of the capillaries. These cases are apparently true Raynaud's disease, the changes in the skin attaining a degree to cause clinical confusion with true scleroderma.

It is apparent that the careful study of the skin capillaries will assist in the differentiation of these cases, but that further study of the primary group is necessary before it will be possible to make any deductions as to the etiologic rôle played by the capillaries.

REPORT OF CASES

Case 1.—A Canadian veterinarian, aged 50, had had a septic infection in 1910. The scleroderma began three years before the patient came to the Mayo Clinic. While driving a car in extremely cold weather, he noticed numbness and pallor of the hands, which persisted in varying degrees. Flexion movements became impaired, and the skin gradually became stretched and shiny. The symptoms were aggravated by cold, but there were no color changes suggesting Raynaud's disease.

At the time of the examination, the hands were cyanotic and cold; the skin was hard and glazed, but not tender. The feet were bluish pink and marmorated. The peripheral arteries pulsated normally. A masklike appearance of the face and partial immobilization of the lip were noted early.

Case 2.—An English farmer, aged 31, first noticed scleroderma during a period of extreme cold three years before coming to the clinic. The first and second fingers of both hands were tender to touch, and it was thought that they were frozen. The toes and ears were similarly affected, and became cyanotic in about three months. There was gradual stiffening of the fingers, followed by pain on motion. The skin became dry and shiny, and, during the last year, the

skin of the face had also become red, hard and shiny. Necrotic areas appeared over the knuckles and elbows and the tips of the fingers.

At the time of examination, the hands and feet were moderately cyanotic, and cold to touch. The skin was tense, hard and shiny, with small dry ulcers on the elbows, and on the middle joint of the third fingers. There was limitation of motion of the fingers and elbows. The skin of the face was firm and had a varnished appearance.

Case 3.—A railroad man, aged 47, an American, had had multiple infections, rheumatic fever, typhoid, influenza, malaria and possibly syphilis. The onset of scleroderma was one year before the patient came to the clinic, when the hands swelled slightly during the summer. Three months later, small ulcers developed on the tips of the fingers, with increasing stiffness of the hand and hardening of the skin. There was slight burning and increased sensitivity of the skin. The process had extended gradually.

At the time of examination, there were well defined, hard, diffuse, sclerodermatous lesions of the hands, feet and arms, anterior chest and abdomen, face and neck. There was no definite pigmentation, and there were no color changes. Motion was impaired 20 per cent. Small trophic areas were present on the tips of the fingers.

Case 4.—A mining engineer, aged 28, an American, first noticed scleroderma during exposure to cold weather two years before coming to the clinic. The skin of the finger tips cracked; the fingers became pale, and, when warmed, were slightly cyanotic. The condition continued with mild color changes when he was exposed to cold, and there was a tendency to cracking of the skin. Six months ago, the hands, ankles and knees began to swell, and since then the swelling has spread to the forearms and legs. These extremities were painful on motion, and the patient felt cold. There was hard swelling in the face, and gradual stiffening of the skin of the hands and face.

At the time of examination, the face was masklike, and the skin hard and shiny. The hands were cyanotic, swollen, hard and cold to touch; the atrophic changes were not marked. Small trophic ulcers of the finger tips were noted. The lesion extended above the elbows, and there was a similar condition in the feet extending to the knees.

Case 5.—An Italian woman, aged 24, had had pleurisy in 1923, and a diminution in menstrual flow for the last three years. The scleroderma began suddenly, twelve years before the patient came to the clinic, with symmetrical asphyxia of the fingers to the first joint. There was no preceding pallor. The condition appeared after exposure to severe cold, and was followed by redness with a burning sensation. The following year, keratoses appeared on the finger tips. During the last five years, the skin had become shiny and stiff, gradually involving the wrists. There was dry necrosis, loss of the terminal joints of the fingers, and increasing general pigmentation, more marked over pressure areas. The skin of the lips, nose and shoulders had become tighter, causing difficulty in movement.

At the time of examination, the skin of the hands and face was hard, glistening, shiny and stretched in appearance. Atrophy was marked. There was some destruction of the terminal phalanges, trophic ulcers of the malleolar and olecranon areas (Fig. 1), and general brownish pigmentation, most marked along spinous processes.

Case 6.—A housekeeper, aged 60, an American, four years before coming to the clinic had had blanching and cyanosis of the fingers to the distal joints, following exposure to cold. There was no pain during the period of recovery, merely a mild sensation of burning. During the last two years, the susceptibility to cold had been more marked. The hands and feet had become puffy and felt uncomfortable, and flexion of the hands was slightly impaired.

At the time of examination, the hands were red, swollen and slightly shiny. Flexion was incomplete. Slight induration extended to the elbows. Venipuncture revealed definite hardening of the skin. Small, dried, necrotic areas

in the tips of the fingers were found. Exposure to cold caused pallor and cyanosis, followed by the rubor and a burning sensation. The peripheral vessels were palpable with normal pulsation, and the blood pressure was 138 systolic, and 84 diastolic.

Case 7.—A telephone operator, aged 26, an American, first noticed color disturbances in the hands six months before coming to the clinic, during a nervous breakdown from overwork. Two months later, she noticed that the hands turned white on exposure to cold, and that the feet and hands became swollen. The skin was shiny, and there was difficulty in flexion. Cyanosis would follow blanching spells, and then redness with burning, and a disagreeable sensation similar to chilblains. Two months later, pain developed during the period of syncope.

On examination, the skin of the hands was found to be shiny and glazed in appearance. The skin of the feet was slightly firm to touch. There was about 75 per cent. flexion in the hands. No atrophic changes in the skin were noted. At room temperature, the hands were red and cool. With colder temperatures, the fingers became mottled with pallor and cyanosis. The peripheral vessels were palpable with normal pulsation.

Case 8.—An American housewife, aged 27, had a nervous breakdown on the day of her husband's death, three years before coming to the clinic. Her voice became hoarse, and she could not speak above a whisper. Swelling appeared in the fingers, with a dead, numb feeling, and, on exposure to cold, the second finger of the left hand turned white to the first joint. There was no pain. Syncope attacks continued, and affected all the fingers during cold or wet weather, but not the thumbs. Later, cyanosis followed the blanching, then redness with deep seated soreness, which felt as if it were in the bone. The skin had become firmer, and complete flexion of the hands was not possible. The patient complained of a sensation of full distention in the hands, and a similar, but more marked, sensation in the feet.

At the time of examination, the skin of the hands was shiny and felt slightly stiff, but was not boardlike or dense. There was no atrophy, but the hands were somewhat cyanotic and cold to touch. They became slightly pale with temperature changes, then presented a bluish, mottled appearance, followed by irregular distribution of red areas. The color changes were not complete. The peripheral vessels were palpable with weak pulsation.

Case 9.—A man, aged 29, an American, had scleroderma which began after a severe shock in a railroad accident. The patient first noticed loss of sensation in one finger on exposure to cold, followed by minor degrees of cyanosis and rubor. This condition persisted, but without pain. Two years later, the hands and feet became swollen and tense. Color changes were more pronounced, and varied with cold and exercise. Recently, the hands and feet had become pale and cold, and color changes became more marked with lesser degrees of cold. It was difficult to flex the hands, and the fingers were swollen and rather firm. There was no atrophy. A dry trophic area was noted on the right thumb. A mild tingling and numb sensation accompanied exposure to cold.

Case 10.—An American housewife, aged 26, had always noticed blanching of the fingers on exposure to cold. Ten months before coming to the clinic, she noticed a transitory cyanosis of the finger tips, extending to the distal joint; the attacks lasted about fifteen minutes. There was no distinct pain, but numbness and color changes were noted. The condition was aggravated by cold, being particularly bad during cold, damp weather. For the last three months, the patient had had transitory edema of the face. No trouble had been noticed in the feet.

Examination revealed the facial lesion to be disseminated lupus erythematosus. There were small trophic changes in the tips of the fingers, with slight loss of tissue and small, dried ulcerations. The skin of the hands was firm and slightly thick. There was no atrophy of the skin, which was pale and cyanotic.

AN ACUTE FEBRILE PLEIOCHROMIC ANEMIA WITH HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES

AN UNDESCRIBED DISEASE *

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This case is remarkable, clinically and anatomically.

REPORT OF CASE

History.—K. Z., a girl, aged 16 years, was an elementary school graduate, had gone to business school, and had been employed for eight months preceding the illness. There were three other children, two younger and one older; all apparently were perfectly normal. There were no home difficulties, and poverty was not extreme. She had spent September 4 and 5 at Rockaway Beach, where she appeared in perfect health and spirits. She had returned home on the evening of September 5 and slept well. On the morning of September 6, she complained of weakness in the upper extremities and had pain on moving the wrists and elbows; she already had marked pallor and was slightly constipated. The symptoms increased in severity until she was admitted to the Beth Israel Hospital, September 15. While at home, she had a constant fever, the temperature rising once to 104 F. and staying at other times between 101 and 102. F.

Physical Examination.—The patient was a pale girl with "café au lait" tinge. A few petechiae were present on the left arm. The lungs and heart revealed nothing abnormal. The spleen and liver were not enlarged. The abdomen was lax and not tender. September 18, the red blood count was 1,330,000; the hemoglobin, 40 per cent.; the leukocytes, 12,600, of which 65 per cent. were polymorphonuclears. The red cells revealed a central pallor, but there were no nucleated elements. A fragility test showed hemolysis to begin at 0.8, and to be complete at 0.19 (?). No platelet count was made. September 19, the red blood count was 1,120,000; the hemoglobin was 40 per cent., and the leukocytes were 19,000. A blood culture remained sterile.

The urine showed marked traces of albumin with hyaline and granular casts. The blood chemistry, September 16, showed: urea, 21.2 mg. per hundred cubic centimeters; nonprotein nitrogen, 31.25 mg. per hundred cubic centimeters, and creatinin, 1.1 mg. per hundred cubic centimeters. The feces and gastric contents gave a marked reaction for occult blood.

Roentgen-ray examination of the chest showed nothing abnormal. The electrocardiogram showed inversion of the T wave in Lead III. The temperature, on admission, was 101.8 F. During the week the patient was in the hospital, it ranged between 100 and 102 F. The pulse varied between 100 and 130. The respiration was around 20. The systolic blood pressure was 130, and the diastolic, 60.

September 19, there was partial paresis of the left arm and leg; also, a slight facial paralysis. The following day, a double Kernig reflex was noted. That night there was pulmonary edema, which responded to treatment. Soon after, the patient went into coma; respirations became irregular, and she died, September 20. Dr. E. Libman, who saw this patient in consultation, recognized the condition as a new disease.

* Read before the New York Pathological Society, Feb. 7, 1924.

Necropsy.—A partial necropsy was done. The body was pale and poorly nourished. The lower lobes of both lungs showed marked congestion. The heart was slightly enlarged; the left ventricle was hypertrophied; the muscle was firm and pale. The mitral and aortic valves were normal. The liver was slightly enlarged, pale and fatty; there was slight nutmeg change. The spleen measured 11 by 8 by 3 cm., and weighed 165 gm. The surface was smooth. On section, the organ was deep mahogany red, somewhat soft and velvety. The malpighian bodies were prominent. The kidneys were large; the capsules were smooth and not adherent; on section, the organ was deep red.

The anatomical diagnosis was anemia; acute congestion at the bases of both lungs; hypertrophy of the left ventricle of the heart; hyperplasia of the spleen, and congestion of the liver and the kidneys.

Microscopic Examination.—The lungs were edematous; at the bases, there was congestion of the parenchyma. The heart muscle revealed a striking

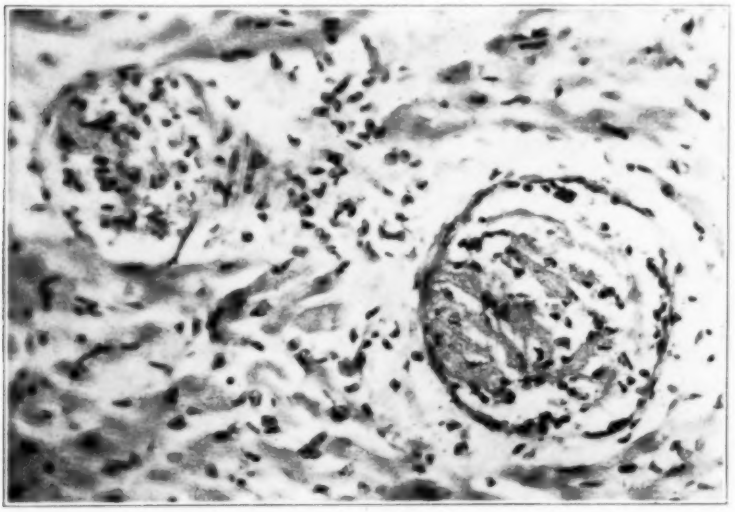

Fig. 1.—Section of heart muscle, showing hyaline thrombi in early stage.

appearance. With the low power of the microscope, practically every field revealed from one to a dozen structures that were unquestionably thrombi in the terminal arterioles or capillaries. These varied in appearance and revealed progressive changes depending on the amount of organization that had taken place. The earliest (Fig. 1) showed merely a plugging of the vessel with a hyaline mass which either partially or completely filled the lumen. Usually, even in this stage, the plug, if not in intimate contact with the wall of the vessel, was surrounded by a layer of flat cells of the fibroblastic type which was distinct from the endothelial intima. In older plugs (Figs. 2 and 3), fibroblasts penetrated into the hyaline mass, and the older the plug, the greater became the amount of fibroblastic infiltration at the expense of the hyaline material; eventually, a small fibroblastic tubercle-like structure was formed. In some of these thrombi, the origin of these fibroblasts from the endothelium of the vessel was plainly discernible. At the same time, the process of organization within the lumen was accompanied by a fibroblastic process around the wall of the vessel in concentric fashion; with the van Gieson stain, some gave the reaction for fibrous tissue. Karyo-

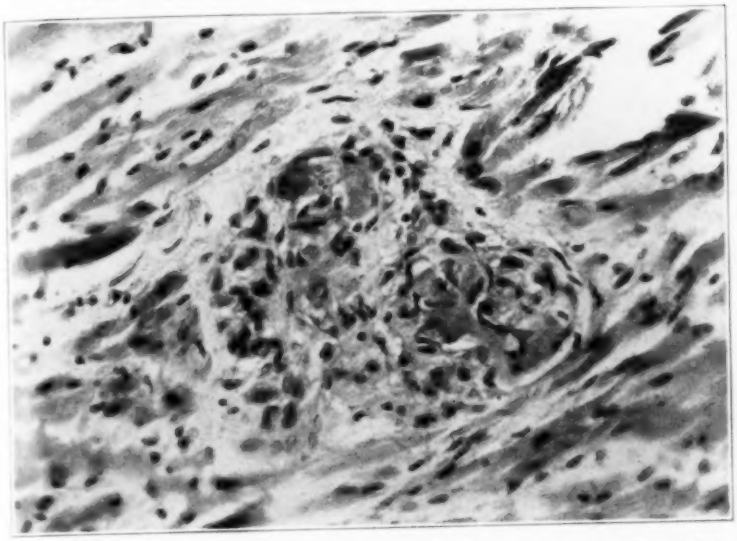

Fig. 2.—Section of heart muscle, showing hyaline thrombi with beginning organization.

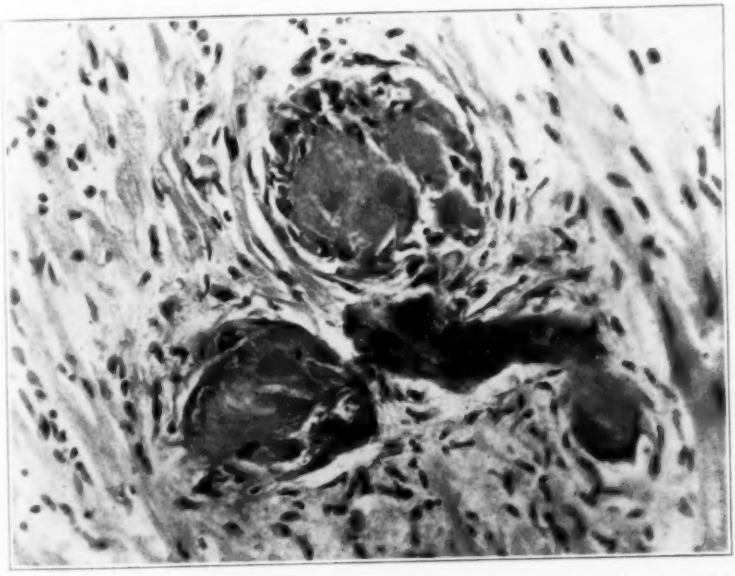

Fig. 3.—Section of heart muscle, showing hyaline thrombi with beginning organization.

kinetic figures in these fibroblasts were common. In some vessels in which the plug had not completely filled the lumen, tiny spaces were formed in which fresh red cells were visible. Only the terminal arterioles and capillaries were involved. The larger vessels with well defined muscular walls showed no change whatever, either in the form of thrombosis or changes in the intima. Every section of heart muscle was involved, the ventricles, the auricles, the papillary muscles and the septum; they were even visible in some of the vessels of the precordial fat. In addition, there was moderate edema of the parenchyma. The liver showed a moderate fatty infiltration and slight congestion around the central veins. Very few hyaline thrombi in the early stages were noted. The spleen showed enormous congestion of the sinuses. A few hyaline thrombi were present in some of the central vessels of the malpighian bodies. The kidneys showed marked parenchymatous degeneration in the tubules and congestion of the parenchyma. The malpighian tufts were

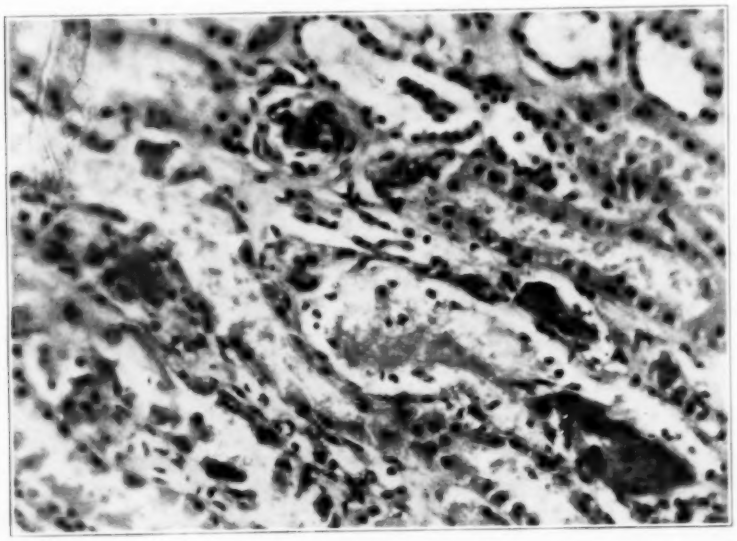

Fig. 4.—Section of kidney, showing hyaline thrombi in terminal arterioles.

clear. Many of the arterioles and capillaries in the middle zone, in the region of the vasa recta, showed hyaline thrombi of the same morphology as those in the heart (Fig. 4). No bacteria, tubercle bacilli or spironema pallida were found in any of the tissues.

A fairly complete search of the medical literature fails to reveal a case resembling this, either clinically or anatomically. Hyaline thrombi have long been recognized but never in respect to the enormous spread and distribution revealed in this case. Klebs [1] apparently was the first to describe these thrombi; he noted them in cases of extensive burns. They have been described in a wide variety of conditions. Thus, Kaufman [2] found capillary red cell thrombi in cases of mercury poison-

1. Klebs: Handb. d. path. Anat. Berlin, **2**:114, 1868-1880.
2. Kaufman, quoted by Dietreich (Footnote 6).

ing. Schmorl[3] found them in the stomach and liver after abrin poisoning. Flexner[4] noted such thrombi in the neighborhood of ulcerated typhoid ulcers of the ileum and in the lung, associated with bronchiectasis; also in the liver in enclampsia, and in the stomach after carbolic acid poisoning. He also states that they have been found in pneumonia, diphtheria and in some of the acute infectious diseases. Loeb, Stricker and Tuttle[5] noted red cell thrombi in the lungs of animals after the injection of a foreign serum. Dietreich[6] found such thrombi in animals after the injection of an extract from beans. Bacterial infections are common causes of such thrombi, for they have been produced experimentally, in infections, by the hog cholera bacillus (Boxmeyer[7]), the pneumococcus and the staphylococcus aureus.

The true pathogenesis of hyaline thrombi was not known until Flexner showed that they arose from agglutinated red cells. This he proved by injecting the highly agglutinative substance, ricin, into rabbits. He concludes that when red cell thrombi are old or when agglutination is compact, they have the appearance of hyaline thrombi. He also states that poisons that destroy red blood corpuscles rapidly provoke agglutinative thrombi, and that the so-called fibrin ferment thrombi are probably agglutinative thrombi. Pearce,[8] indeed, obtained hyaline thrombi in the liver associated with focal necroses by injecting agglutinating serums. He also injected filtered autolyzed products of various bacteria which possess hemagglutinins of low activity and obtained similar necroses of the liver associated with fused red blood cell thrombi, i. e., structures resembling hyaline thrombi.

In this condition, it is interesting to note that, as far back as 1875, Landois[9] found that an injection of foreign blood causes multiple capillary thrombosis.

I have learned that Dr. Max Lederer of Brooklyn has seen four cases clinically identical with the one described in this report. He permits me to state that, thus far, no cause has been found, and that all four patients recovered promptly after a single transfusion of blood.

From these observations we conclude that death, in the case described, resulted from some powerful poison which had both agglutinative and hemolytic properties. If opportunity offers, further investigation will be made of this strange disease with strange pathologic morphology.

3. Schmorl: Jahresb. d. Gessellsch. f. Nat.-u. Heilk. in Dresd., 1899-1900, quoted by Flexner (Footnote 4).
4. Flexner: J. M. Res. **8**:316, 1902.
5. Loeb, Stricker and Tuttle: Virchows Arch. f. path. Anat. **201**:5, 1910.
6. Dietreich: Centralbl. f. Path. **23**:372, 1912.
7. Boxmeyer: J. M. Res. **9**:146, 1903.
8. Pearce and Winne: Am. J. M. Sc. **128**:669, 1904.
9. Landois: Die Tranfusion des Blutes, Leipzig, 1875, p. 225.

THE VITAL CAPACITY IN ARTIFICIAL PNEUMOTHORAX

THE MECHANISM AND THE FACTORS MODIFYING THE VITAL CAPACITY, WITH ESPECIAL REFERENCE TO ITS CLINICAL AND PROGNOSTIC VALUE IN THE COLLAPSE THERAPY *

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That a certain relation exists between the degree of structural involvement of the lung tissue and the diminution in the vital capacity has been known since Hutchinson [1] published his observations on the vital capacity in a great variety of subjects, but that the recuperation of pulmonary function seems to be possible even when the integrity of the lungs is not perfect is of great clinical importance and deserves more extensive investigation. The various functional modifications of the respiratory capacity taking place during the entire course of therapeutic pneumothorax afford a great deal of information in this respect.

A priori one would expect a quantitative relation between the amount of air introduced into the pleural cavity and the diminution of the vital capacity. Such, however, was not the case in many of our tuberculous cases treated with artificial pneumothorax; the same quantity of air introduced into the pleural cavity produced different results in the reduction of the vital capacity not only in different cases, but even in the same case at various insufflations. It follows that the amount of air introduced into the pleural cavity is not the sole factor affecting the decrease in the vital capacity, but many other factors come into play. It varies with the type of pneumothorax, with the functional and pathologic status of the treated lung, as well as the condition of the contralateral lung, with the movements of the diaphragm and mediastinum, and with the cardiac ability to compensate. Each of these factors has a definite bearing on the vital capacity, and may affect it jointly or singly.

It was the purpose of these experiments to find out which of the factors plays a more important rôle in the reduction of the respiratory capacity, what clinical assistance we can derive from the periodic vital capacity measurements as to the amount of gas to be administered at each insufflation, and how much spirometry can serve as a prognostic criterion in the collapse therapy.

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* From the Montefiore Hospital, Bedford Sanatorium for Incipient Tuberculosis.

1. Hutchinson, J.: On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise Method of Detecting Disease by the Spirometer, Med.-Chir. Tr. **29**:137, 1846.

MODIFICATION OF VITAL CAPACITY IN VARIOUS TYPES OF ARTIFICIAL PNEUMOTHORAX

In considering the vital capacity changes that take place with each injection of air into the pleural cavity, the distinction between the types of pneumothorax existing at the time of insufflation must be kept clearly in mind. In a previous article,[2] I indicated that at least three distinct types of induced pneumothorax exist with reference to the undiseased portion of the lung:

(*a*) Expansile pneumothorax, in which the intrapleural pressure is much smaller than the intrapulmonary pressure and the lung is not compressed, but collapsed or retracted by virtue of its own elasticity, and still

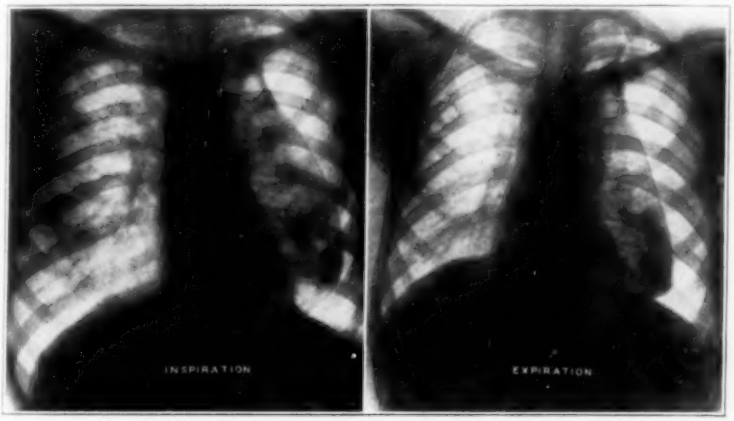

Fig. 1.—Inspiration and expiration, respectively, showing a definite expansion and contraction of collapsed lower left lobe taking place with each respiratory movement, while the compressed upper part of upper lobe remains unchanged during both respiratory phases. Both inspiratory and then expiratory intrapleural pressures were negative in this case.

expands and contracts to a limited extent with each respiratory phase (Fig. 1).

(*b*) Static pneumothorax, or pneumothorax of rest, in which the intrapleural pressure equals that of the intrapulmonary pressure; i. e., both are at atmospheric pressure, and the collapsed lung is in a state of equilibrium or permanent rest (Fig. 2).

(*c*) Compression pneumothorax, in which both the inspiratory and expiratory intrapleural pressures exceed that of the intrapulmonary one and the lung is actually compressed, its entire volume being changed and its air capacity reduced to the minimum (Fig. 3).

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2. Bendove, R. A.: The Classification of Artificial Pneumothoraces and Their Corresponding Clinical Value, Am. Rev. Tuberc. **10**:540 (Jan.) 1925.

(*d*) There exists another type of pneumothorax that cannot be included in the foregoing classification, namely, localized pneumothorax, i. e., a small pocket of air in the pleural cavity surrounded and limited by strong pleural adhesions. In such pneumothorax only the immediate lung tissue is compressed slightly, but the rest of the lung keeps on functioning as before, irrespective of the high pressure created in this localized pneumothorax (Fig. 4).

Obviously enough, all other factors being equal, the same amount of air introduced in any one of these pleural cavities will occasion different changes in the vital capacity. The smallest variations are noticed in localized pneumothoraces; even such a high positive pressure as + 40

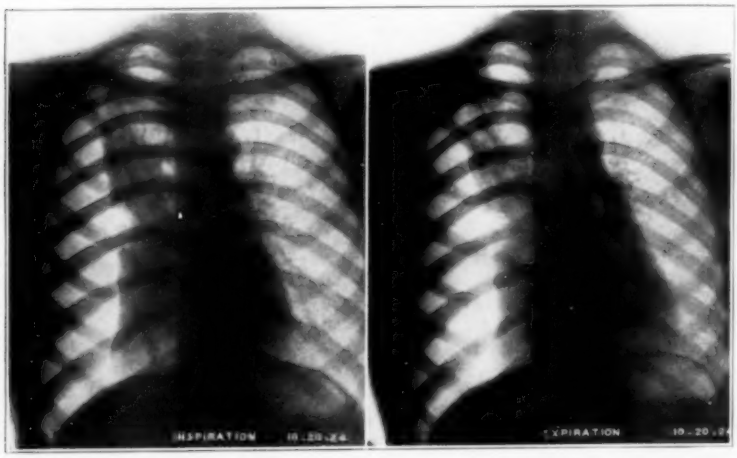

Fig. 2.—Inspiration and expiration, respectively, of a case of right pneumothorax in which the inspiratory intrapleural pressure was equal to the intrapulmonary one. There was no expansion of the lobes of this lung during inspiration. The little movement en masse noticed in this lung is due to the motion of the contiguous organs, particularly that of the mediastinum.

+ 30 mercury entails very little reduction in vital capacity, the reason being that all the pressure is exerted only on this localized cavity, whereas the functioning surface of the lung is not encroached on at all. The same principle holds true in a much larger scale in an established pneumothorax of compression, provided the mediastinum is rigid and cannot be displaced. There is no ingress of air into such a compressed lung, and, consequently, it performs no respiratory function. The only volume of air it contains is the "minimal air" enclosed in the collapsed alveoli from which it is never expelled, and if such a condition exists for a long period of time, this small amount of entrapped minimal air becomes absorbed by the blood and the lung will eventually become

entirely solid (Fig. 6). It follows that, regardless of the amount of air introduced into such a pleural cavity and the positive pressure created therein, the spirometric readings will be changed very little, as the entire respiratory function is carried out by the noncollapsed lung which, in the presence of a rigid mediastinum, is affected to a very limited extent by the pneumothorax. We found that the vital capacity of such cases,

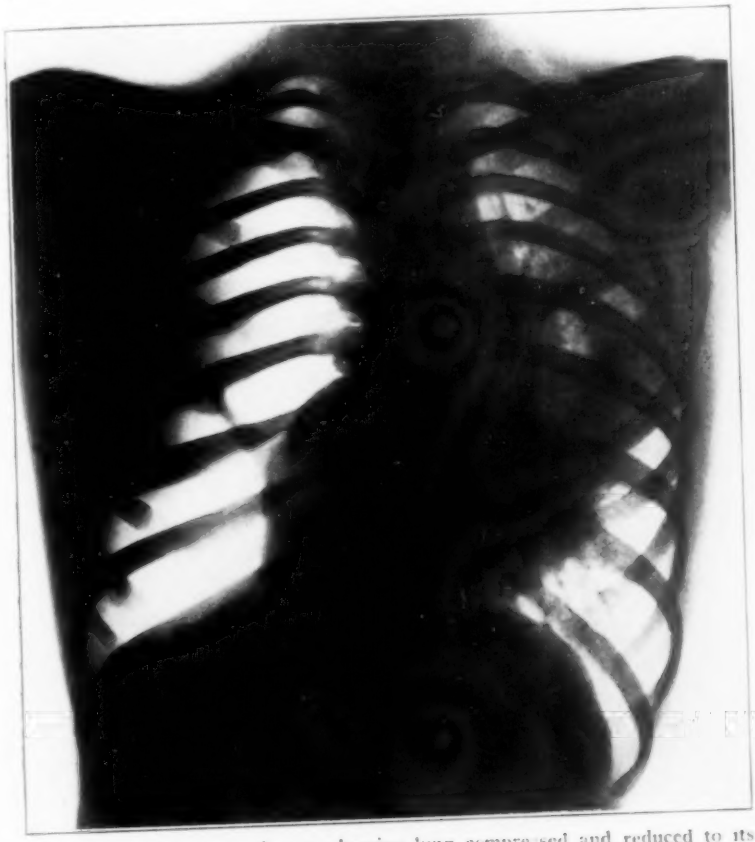

Fig. 3.—Right pneumothorax, showing lung compressed and reduced to its minimum. Both inspiratory and expiratory intrapleural pressures were highly positive.

as a rule, bears no relation to the amount of air introduced with each insufflation.

Static pneumothorax, or pneumothorax of rest, is a transitory phase which any of the other two types of pneumothorax go through at one time or other. In such cases, the vital capacity readings do change with

each insufflation, but these spirometric modifications can be studied more extensively and accurately in expansile pneumothorax, the only type that exhibits a whole series of vital capacity changes during the long course of the collapse therapy. In cases of expansile pneumothorax, each insufflation entailed a reduction in the vital capacity, but

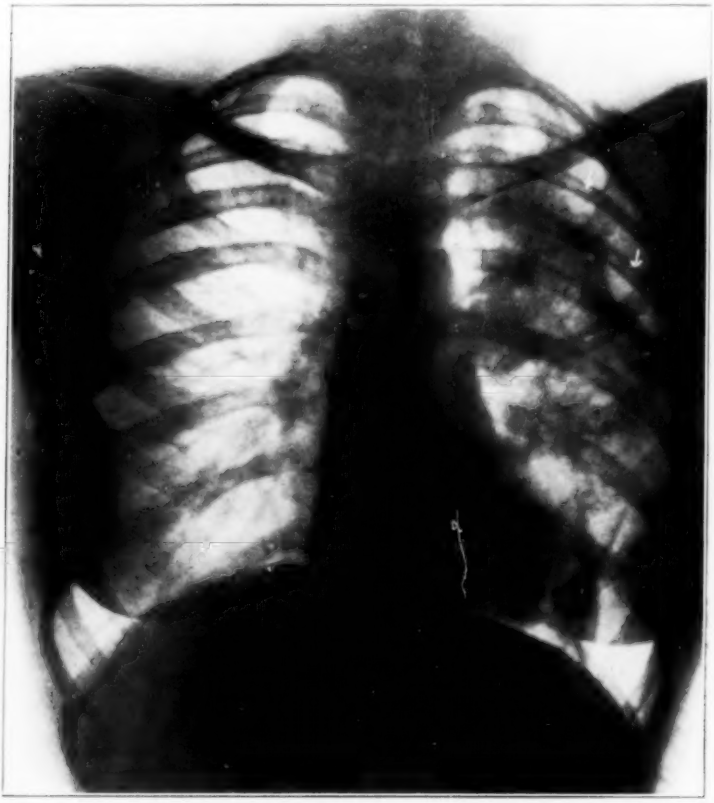

Fig. 4.—Left localized pneumothorax. A few attempts at induction of pneumothorax resulted in the creation of only two small pockets of air in the first and second interspaces, the strong adhesions preventing the separation of the visceral from the parietal pleura.

never to the extent of the amount of air introduced into the pleural cavity. Furthermore, the same amount of air could at one insufflation bring about a different modification in the vital capacity than at a subsequent one. To explain the phenomenon many factors have to be taken into consideration, and of these the *residual air* is of particular importance.

RESIDUAL AIR OF COLLAPSED LUNG AND ITS RELATION TO VITAL CAPACITY

The vital or the respiratory capacity includes in itself the tidal air, the complemental or the most forced inspiratory air, and the supplemental or the most forced expiratory air. But, even after the entire supplemental air has been driven out, there still remains in the lungs 1,000 c.c. or more that is never expelled and is designated as the residual air. Whether there exists a constant between the vital capacity and the residual air has not been determined yet, though they seem to be inversely proportional to each other, i. e., the greater the residual air

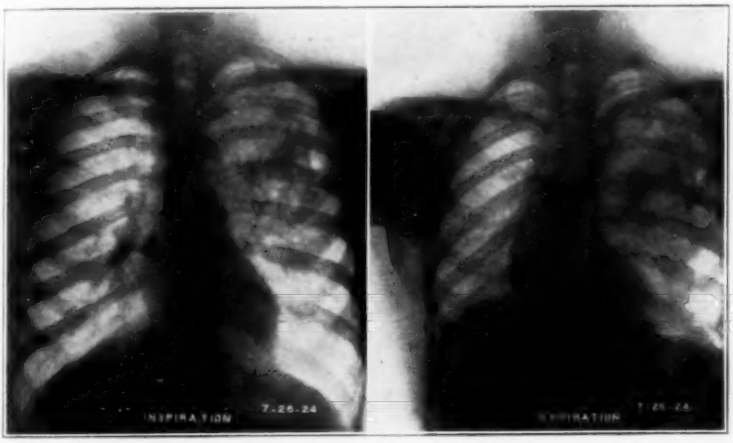

Fig. 5.—Left pneumothorax, showing lower lobe expanding to its full capacity during inspiration, driving all the air into upper part of pleural cavity around the diseased, inelastic portion of lung, and contracting a great deal during expiration. Two hundred cubic centimeters of air introduced into this pleural cavity brought an increase of 100 c.c. in the vital capacity. Larger quantities injected never reduced the vital capacity by more than one third of their own amounts.

the smaller the vital capacity, and vice versa. Lundsgaard and Van Slyke [3] found that the residual air is increased in early cases of pulmonary tuberculosis, and they are of the opinion that this is the cause of the diminution of the vital capacity of such cases. The small vital capacity of emphysematous cases is also explained on the basis of an excessive residual air of the overinflated and poorly elastic lung. On the other hand, it was found that athletes have a high vital capacity and a very low residual air, because the well developed muscles of the chest and, particularly, those of the abdomen press tightly on the abdominal con-

3. Lundsgaard, C., and Van Slyke, D. R.: Studies of Lung Volume, J. Exper. Med. **27**:129, 1918.

tents, which, in turn, push the diaphragm high into the thoracic cavity during expiration and squeeze out most of the air from the basal lobes.

Yet, even after the most forcible expiration, the lungs are far from being entirely collapsed, so long that the thorax remains closed. The reason is very simple: the lung with its contained air, which presses

Fig. 6.—Long standing hydropneumothorax, showing a compressed, almost consolidated left lung, the functional capacity of which is entirely lost. More than 3,000 c.c. was aspirated within a month, but the vital capacity remained as low as before.

against the chest wall, cannot diminish its volume more than the volume of the thoracic cavity, as the expiratory intrapulmonic pressure is always higher than the intrathoracic pressure. Those two antagonistic forces,

i. e., the positive intrapulmonary pressure and the negative extrapulmonary, or intrapleural pressure, keep the elastic lung from being collapsed and emptied entirely. When we introduce gas into the pleural cavity, we gradually loosen this negative tie and allow the lung to collapse on itself, so that not only the supplemental air is expelled during expiration but also a part of the residual air is driven out. This expired residual air, which never participates in the vital capacity of the physiologically functioning lung, becomes an integral part of the vital capacity in expansile pneumothorax and is of clinical importance as it alleviates the dyspnea or prevents it altogether, as will be commented on later. The amount of residual air driven out from the lung stands in direct relation to the rise of the intrathoracic pressure, which is now to be considered.

INSPIRATORY AND EXPIRATORY PRESSURES IN THE INFLATED PLEURAL CAVITY AND THEIR EFFECT ON VITAL CAPACITY

Physiologically, the inspiratory intrathoracic pressure is always more negative than the expiratory pressure; this allows the lung to be much more expanded during inspiration than during expiration. The same holds true in pneumothorax. The expiratory pressure is always greater than the inspiratory pressure, and so long as the latter remains below the intrapulmonary pressure the lung is able to expand with each inspiration, and the more the expansion, the greater is the ingress of air, i. e., the greater is the complemental air. When a certain quantity of air is introduced into the pleural cavity, it increases the inspiratory intrapleural pressure and impedes the expansion of the lung during inspiration, which means a curtailment in the complemental air, and thus a decrease in the vital capacity. This reduction of the vital capacity would probably be equal to the amount of air introduced, were it not for the expiratory intrapleural pressure, which also is increased, compressing the lung more effectively during expiration, and driving out not only the supplemental air but also a part of the residual air. The higher the expiratory intrapleural pressure, the greater is the amount of residual air driven out. We thus have created two conditions in the pleural cavity which work in opposite directions, as far as the vital capacity of the collapsed lung is concerned: one, the increased inspiratory intrapleural pressure, tends to curtail the vital capacity; the other, the elevated expiratory pressure, augments it. The amount of reduction of the vital capacity will be equal to the diminution in the complemental air minus the residual air expelled. Both may be affected simultaneously or either one separately, depending on the new pressures created in the pleural cavity. Thus,

(*a*) If the inspiratory pressure is not reduced very much and the expiratory air is brought slightly above the atmospheric then the vital

capacity will be reduced very little because the complemental air is not reduced much, whereas the positive pressure established in the pleural cavity during expiration exerts itself mostly on the lungs, compressing them and letting the residual air come into play. Case 1 (Fig. 7) illustrates it clearly. The vital capacity prior to the insufflation was 3,100 c.c., and, after the introduction of 600 c.c. of air into the pleural cavity, it decreased to 2,900 c.c., the actual reduction being only 200 c.c., though 600 c.c. was injected. The preinsufflatory intrapleural pressures were —20 —7, and the postinsufflatory ones were —14 +4, i. e., the complemental, or inspiratory, air was not reduced very much, and this

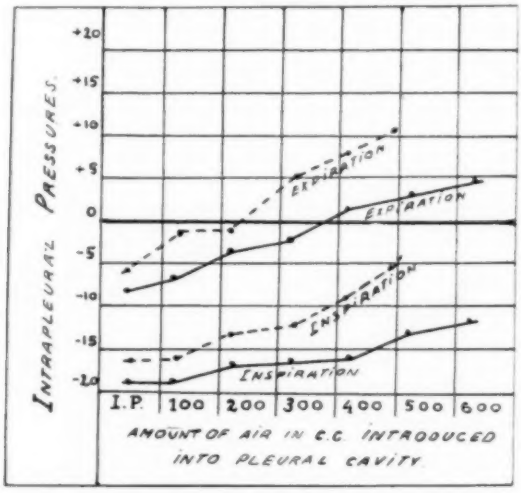

Fig. 7.—Solid line (Case 1): vital capacity prior to insufflation, 3,100 c.c., after insufflation, 2,900 c.c., a reduction of only 200 c.c., although 600 c.c. were introduced; broken line (Case 2): preinsufflatory vital capacity, 2,300 c.c., postinsufflatory vital capacity, 2,000 c.c., a reduction of 300 c.c. after injection of 400 c.c.

curtailment was made up for by the residual air, which was forced out of the lung by the positive expiratory pressure.

(*b*) When the inspiratory pressure is raised to about the atmospheric, which means that practically all the complemental air of the lung has been cut out, then, even in the presence of a high expiratory pressure, the vital capacity will be reduced a great deal (Fig. 7, Case 2). The explanation lies in the fact that even if the entire residual air could have been driven out from the compressed lung during expiration, its amount would always be smaller than the inspiratory complemental air, which has been reduced to a minimum.

(*c*) When the inspiratory pressure is reduced and the expiratory pressure remains more or less stationary, the vital capacity is diminished almost to the amount of air introduced (Fig. 8, Case 3). Such cases usually have a labile mediastinum, which becomes displaced toward the untreated side, encroaching on the respiratory function of the contralateral lung. (This factor is taken up in detail under a separate heading.)

(*d*) In compression pneumothorax in which the lung takes no part in the respiratory function, the preinsufflatory and postinsufflatory vital capacities are always about the same (Fig. 8, Case 4). The difference

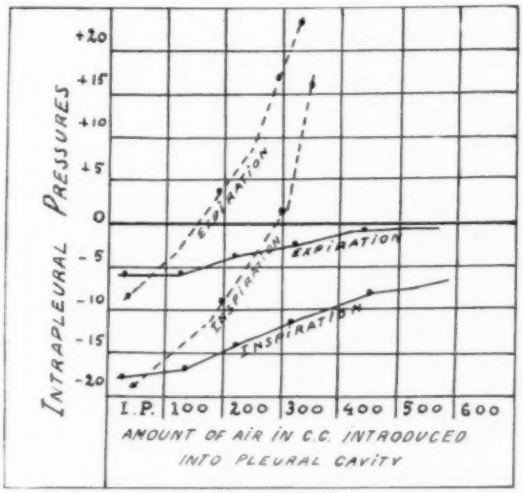

Fig. 8.—Solid line (Case 3): preinsufflatory vital capacity, 2,800 c.c., postinsufflatory vital capacity, 2,400 c.c.; broken line (Case 4): vital capacity before and after insufflation of 1,500 c.c.

between the inspiratory and expiratory intrapleural pressures is simply due to the difference between the dimensions of the hemithorax in inspiration and expiration, and since such patients usually possess a rigid mediastinum that offers the same resistance to the introduced air as the chest wall does, a low negative intrapleural pressure is rendered highly positive very rapidly. This cannot happen in expansile pneumothorax when the lung is still functioning and the pressure of the insufflated air exerts itself first on the lung itself. The resistance which the lung offers to the air introduced into the pleural cavity also varies a great deal with the degree of elasticity which its tissues possess at the time of the insufflation.

HOW VITAL CAPACITY IS MODIFIED BY PATHOLOGIC AND PHYSIOLOGIC STATUS OF COLLAPSED LUNG

The anatomic lung tissue is very elastic and possesses both the expansile and contractile forces to the same degree. Pathologic involvement of the lung may attenuate, injure, and destroy entirely either the expansibility alone, or the contractility alone, or both of them simultaneously. In any infiltrative condition of the lung, the expansibility is the first to suffer while the contractility remains more or less intact; hence, the tendency of such tissue to undergo atelectasis. In emphysema, the reverse takes place; the contractility is attenuated whereas the expansibility is intact, leading to an overinflation. When the infiltrated lung tissue undergoes caseation, it loses all its elastic characteristics, both expansile and contractile, and becomes soft and friable. As the tissue goes through all the gamut of destruction and repair to fibrosis, it becomes hard and unyielding, but with a strong tendency to contract.

The altered histological architecture of the tuberculous lung treated with artificial pneumothorax exhibits, as a rule, all the modified elastic characteristics just enumerated, and consequently it reacts differently to the gas introduced into the pleural cavity. The infiltrated and caseous areas will become compressed at once; the fibrosed areas will yield very slowly, but once "caved in" will remain so all the time; whereas the uninvolved portion of the lung will continue to expand and contract with each respiratory movement. So long as the intrapleural pressure is kept lower than the intrapulmonary pressure, the lung will extend to a limited extent with each inspiration, but as soon as the inspiratory intrapleural pressure reaches that of the intrapulmonary one, the expansibility of the lung tissue cannot assert itself any more, and the lung remains compressed even during inspiration. If such a high positive intrapleural pressure is maintained for a long time, the expansibility of the lung tissue may become injured and never regain its former physiologic limit. In expansile pneumothorax, however, we always leave the intrapleural pressure below the atmospheric, and the uninvolved portion of the lung continues, therefore, to function within certain confines during the entire course of the treatment.

It should be taken into consideration that the diseased, edematous alveoli contain very little air and much less pressure is required to render them entirely airless and close them up completely. Consequently, there is no access of air into such alveoli, and they cease to dilate with each inspiration, it being one of the main desideratum of pneumothorax therapy to keep the diseased alveoli from to and fro motion synchronous with the respiratory movements. As we progress in the course of therapy by collapse of the lung, these atelectatic alveoli become fibrosed and fail to reinflate, even in the most forcible inspiration; they remain permanently compressed and contracted. A most interesting phenomenon

occurs when gas is introduced into such a pleural cavity. The gas accumulates mostly around these diseased areas, no matter where they are situated in the upper or lower lobes, during inspiration, while, in expiration, the gas is distributed evenly from apex to base. Figure 5 exhibits this phenomenon saliently. The explanation offered is that there is no access of air into the diseased, contracted areas of the upper lobe, during inspiration, whereas the lower uninvolved lobe inflates freely with the inspiratory movement and replaces the air in the empty space left by the contracted tissue; during expiration, on the other hand, this functioning part of the lung becomes also collapsed and the air distributes itself evenly throughout the pleural cavity.

What is of greatest interest, as far as spirometry is concerned, in such cases is the fact that a small amount of air introduced into the pleural cavity brings about a slight increase in the vital capacity instead of a decrease. In the case just cited, an introduction of 200 c.c. entailed, as we anticipated, an increase of about 100 c.c. in the vital capacity. The explanation is to be sought in the mechanicodynamic forces created in this hemothorax; during inspiration, all the dimensions of the thorax increase and the uninvolved elastic part of the lung expands freely, driving all the air into the vacant area left by the nonfunctioning, contracted portion of the lung; whereas, during expiration, the functioning portion recoils on itself, and all the diameters of the thorax decrease and exert an equal pressure throughout, so that the air becomes evenly distributed and forces the residual air from this functioning portion of the lung. If, however, the amount of air insufflated is being increased, it begins to encroach also on the inspiratory expansion of the functioning portion of the lung, cutting short its complemental air. This impediment of expansion stands in direct relation to the amount of air introduced and the inspiratory intrapleural pressure created. Should a high intrapleural pressure be maintained for a long period of time, keeping the uninvolved part of the lung in compression, its expansile force becomes inhibited or greatly injured, and, of course, a reduction of the vital capacity ensues. That is why it is much better to give smaller amounts with lower intrapleural pressure, repeated quite frequently, than to give large amounts with a high intrapleural pressure.

Once the expansibility of the lung tissue has been inhibited or injured, it can never be regained. The contractile force preponderates and its tendency to atelectasis is augmented. Thus, we have patients treated with artificial pneumothorax under high intrapleural pressure; their lungs, having been kept compressed for months, were allowed to expand gradually, by reducing the insufflatory amounts and the intrapleural pressure. Such patients gain gradually in their vital capacity, but every insufflation curtails their vital capacity much more than the amount of air introduced into the pleural cavity, because of the marked

tendency of this lung tissue to undergo atelectasis. But, after a few days, particularly if they are made to breathe deeply, they regain the former amount of vital capacity. This shows that their expansibility has not been permanently injured, but has been greatly attenuated by the long standing compressed condition. However, those lungs which have been kept compressed for many years fail to re-expand, and the vital capacity of the patients is at a low ebb. Fluid causes even a greater injury to the expansibility of the lung tissue and, if not removed in time, may occasion a permanent compression of the lung and a complete reduction of its respiratory capacity (Fig. 6).

TEMPORARY AND PERMANENT EFFECT OF PLEURAL EFFUSION ON VITAL CAPACITY

As already intimated, the extent, character and permanence of the loss of the expansile quality of a compressed lung stands in direct relation to the nature and the duration of the underlying cause, hence the longer the fluid is left in the pleural cavity, the greater injury will it inflict on the expansibility of the lung tissue and, therefore, also on the vital capacity. The chart (Fig. 9, Curves 1 and 2) of cases of hydropneumothorax illustrates lucidly that not only the fluid, but also, to a greater extent, its duration in the pleural cavity causes a marked crippling of the respiratory capacity of the lung. Curve 1 represents a case of pleural effusion of more than a year's duration. Before aspiration, the vital capacity of the patient (a man) was 2,200 c.c., and the withdrawal of 1,800 c.c. of thick, yellow fluid, replaced by 800 c.c. of air, brought no change in the vital capacity. Daily spirometric readings for four consecutive weeks disclosed no essential changes (the small changes noticed on the chart are due to the physiologic variations observed in any serial spirometry). At the end of three weeks, the pleura was insufflated with 300 c.c. of air; it gave rise to a high intrapleural pressure, but no alteration in the vital capacity took place.

Curve 2 exemplifies the effect of the timely removal of fluid from the pleural cavity on the rapid recuperation of the respiratory capacity of the lung. This was a case of hydropneumothorax of about two months' duration. The vital capacity of the patient (a man), before aspiration, was 2,000 c.c. After the withdrawal of 1,400 c.c. of clear fluid and its replacement by 800 c.c. of air, the vital capacity increased to 2,200 c.c. Daily spirometric readings showed a gradual but persistent increment of the vital capacity, so that at the end of three weeks it reached 2,800, i.e., an increase of 800 c.c., almost half the amount of his vital capacity prior to the aspiration. When 500 c.c. of gas were now introduced into the pleural capacity, it occasioned a reduction in the vital capacity to the same amount. This seldom happens in other cases of expansile pneumothorax. However, in four days, the vital capacity returned to what

it was before the induction of gas. The vital capacity modifications in the subsequent refills did not differ in any way from those described under expansile pneumothorax.

In Case 1, the compressed lung, under the fluid for more than a year, became completely atelectatic and probably fibrosed, lost its elasticity and could not expand any more, even after the removal of the primary cause. In Case 2, the elasticity of the lung did suffer slightly under the pressure of the fluid, but, as soon as the cause was removed, it took a comparatively short time for the atelectanic lung to regain its expansibility, gradually but persistently, the vital capacity keeping pace with it.

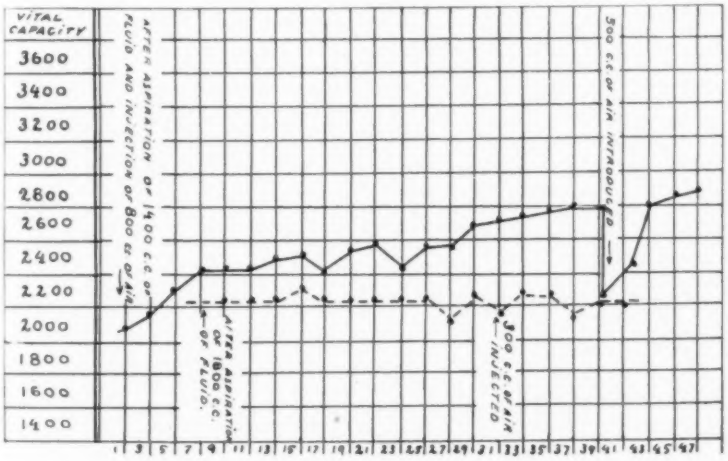

Fig. 9.—Broken line: case of left pleural effusion of about one year's duration, showing no change in the vital capacity after aspiration; solid line: case of right hydropneumothorax of about two months' duration, showing a gradual increase in the vital capacity after aspiration.

This is the best argument in favor of aspirating pleural fluid as soon as possible and replacing it by air, which is much easier to manage, exerts less compression on the lung, and is absorbed much more quickly.

Furthermore, fluid always gravitates to the bottom, compressing the basal lobe, no matter whether it is diseased or not, whereas air distributes itself according to the existing pneumodynamics, which makes it accumulate mostly around the diseased areas.

It is worthy of notice that, even when we replaced the aspirated fluid with the same amount of air, the vital capacity was invariably greater than before aspiration. This might be attributed to the greater compressibility of air than fluid and to the fact that air can be made to occupy less space during inspiration, allowing the lung to expand and breathe in more air with each inspiratory phase.

MOVEMENTS OF DIAPHRAGM AND MEDIASTINUM WITH REGARD TO VITAL CAPACITY OF COLLAPSED AND CONTRALATERAL LUNGS

The relation of the movement of the diaphragm to the vital capacity will be reported in a separate contribution on phrenodynamics of which we are now making a special study. Suffice it to mention here that when the diaphragmatic function is not injured it assists a great deal in increasing the vital capacity by compressing the lower lobe during expiration; this is particularly true when the basal lobe is the only functioning one. In case of paralysis of the diaphragm, a part of the air injected into the pleural cavity is wasted by keeping it down at a lower level than its physiologic one, and it should be taken into consideration by the operator when insufflations are made.

The rôle of the mediastinum, in artificial pneumothorax, has been discussed fully in my work on the classification of artificial pneumothoraces and their corresponding clinical value,[2] to which the reader is referred. Its mobility has little bearing on the vital capacity of the collapsed lung, but it is one of the chief factors in modifying the vital capacity of the untreated lung. If it is very rigid and stable, it never becomes deflected into the contralateral side, no matter how high the intrapleural pressure is raised, and, consequently, no encroachment is made on the respiratory surface of the other lung. But if the mediastinum is labile, it becomes displaced into the other hemithorax; the higher the intrapleural pressure, the greater is the displacement and the more is the embarrassment of the contralateral lung. In the presence of a labile mediastinum, no compression pneumothorax can be obtained without causing marked respiratory distress and dyspnea, not only because of the marked reduction of the vital capacity of the treated lung, but also on account of the compression of the other lung, caused by the displaced mediastinum and diminishing its respiratory capacity.

We had a case of a right spontaneous pneumothorax in which the mediastinum was thrust beyond the nipple line of the other hemithorax (Fig. 10). The patient was very orthopneic and his vital capacity was, at that time, only 800 c.c. Only after the withdrawal of 1,000 c.c. of air from the pleural cavity could he lie on his back without gasping for air, though the intrapleural pressure still remained slightly positive, and the pneumothorax lung was entirely compressed. His vital capacity was then 1,200 c.c. Fluoroscopically, we observed that the collapsed lung did not function yet, but that the mediastinum was moved more toward the median line, proving beyond doubt that the 400 c.c. increase of the vital capacity came from the contralateral lung, which was now relieved from the pressure of the previously displaced mediastinum.

Fortunately, most of the patients treated with artificial pneumothorax that require a high intrapleural pressure because of unyielding cavities,

abundance of fibrosis and pleural adhesion, have, as a rule, a rigid mediastinum, and therefore a compression pneumothorax can be obtained without encroaching on the respiratory capacity of the contralateral lung. In expansile pneumothorax, in which the intrapleural pressure is always negative, there is very little deviation of the mediastinum to the other side, and the reduction of the vital capacity of the noncollapsed lung is

Fig. 10.—Right spontaneous pneumothorax with considerable displacement of the mediastinum to the left side. The vital capacity, at this time, was 800 c.c. After aspiration of 1,000 c.c. of air from the pleural cavity, the inspiratory intrapleural pressure still remained slightly positive, but the mediastinum was moved toward the median line and the vital capacity increased to 1,200 c.c.

negligible. The relations of the amount of air introduced with each insufflation to the amount of air curtailed of the vital capacity will then depend only on the treated lung, and will show all the modifications of the vital capacity, as explained before. However, when the expiratory intrapleural pressure reaches about zero, in the presence of a very labile

mediastinum, then the vital capacity will be diminished to the same amount of air introduced into the pleural cavity, because the other lung also is then being encroached on by the displaced mediastinum.

Though the mediastinum is one of the main factors affecting the vital capacity of the contralateral lung, the compensatory ability of the heart and the development of vicarious emphysema are the determining factors in this respect.

INFLUENCE OF HEMODYNAMICS ON VITAL CAPACITY OF COLLAPSED AND NONCOLLAPSED LUNG

The interdependence of the circulatory and the respiratory systems is so intimate that any change occurring in one of them is invariably followed by certain changes in the other one. Thus, in case of heart failure, the lung is first to suffer from a venous stasis, and, when an obstruction occurs in the pulmonary circulation, the heart is first to respond to it by a dilatation or hypertrophy of its right ventricle.

The resistance of pulmonary circulation is governed a great deal by the degree of lung expansion; both hyperdistention and compression of the alveoli interfere with the circulation of the blood in the pulmonary capillaries. Hypertrophic emphysema furnishes a good illustration of impaired pulmonary circulation because of overdistention of the alveoli the walls of which become thinned out, pressing on the capillaries and impeding the blood flow therein, which impediment leads to a dilatation and hypertrophy of the right side of the heart. As an example of interference with the pulmonary circulation because of compression of the alveoli could be cited pleural effusion or pneumothorax.

The degree of interference with the circulation in the collapsed lung runs parallel with the amount of compression to which the alveoli are subjected, and accordingly the pulmonary circulation is disturbed much more in compression pneumothorax than in expansile pneumothorax. So long as the blood vessels of the collapsed lung are still patent, the blood continues to flow through them, though their tension is very high, but, when they become entirely obliterated, the blood stream must, of course, be diverted to other channels or blood vessels. But, in order not to disturb the equilibrium maintained between the systemic and pulmonary circulations, the heart has to increase its action and propel the same amount of blood in the same unit of time through the reduced capillary surface. If the reserve power of the heart is not damaged, it compensates well and increases its action, which leads to a dilatation and hypertrophy of the right ventricle or the entire heart, but if the cardiac muscles have been damaged by the long and persistent tuberculous toxemia, it fails to compensate and stasis takes place in the pulmonary circulation.

Underhill,[4] in experimenting with ligating one of the pulmonary vessels in animals, found an increase in the blood pressure of the carotid, and he interprets this rise in the systemic blood pressure as a compensation of the heart because of deficient oxygenation. But, if the animal was fatigued and exhausted, a fall in the carotid blood pressure was noticed on ligation of the pulmonary vessels, which meant that the heart was unequal to the strain put on it, and could not send out the same quantity of blood in a given time through one lung only.

The same phenomena we noticed in our patients treated with artificial pneumothorax; some of them showed an increase in the systemic blood pressure after deflation of one lung, and some of them showed a decrease in blood pressure. Those who showed a higher blood pressure after the induction of pneumothorax exhibited also an enlargement of the diameters of the heart, seen distinctly on the roentgenograms. Such patients, as a rule, had only a slight diminution in their vital capacity and, even if the decrease was marked after the first few insufflations, it recuperated gradually and persistently. But those patients who showed a lower blood pressure after pneumothorax exhibited either no change in the size of the heart or it became even smaller, and their vital capacity fell greatly after first insufflations and seldom returned to its former volume.

Rubow[5] found a decrease of the vital capacity in all cardiac cases, and one of the main causes, he thinks, is that the lung tissue is rendered rigid and inelastic by the capillary vascular turgescence, and dilatation and contraction of the lung are thus interfered with. Another reason given is the protrusion of the distended capillaries into the alveoli, which decreases their volume of air. The same is probably true of the lung tissue and the capillaries, in cases treated with artificial pneumothorax for the first few days. But, if the heart compensates well and a vicarious emphysema develops, not only in the contralateral lung but in the functioning portion of the collapsed lung as well, the respiratory capacity reestablishes gradually; whereas, if the exhausted heart fails to compensate against the increased resistance in the pulmonary circulation, a stasis ensues, and a marked fall in the vital capacity remains permanent.

It is obvious that the degree of compensation demanded of the heart is directly proportional to the amount of compression of the lung; hence, in those patients whose hearts become anemic and exhausted by the chronic tuberculous toxemia, the deflation of the lung should be done very gradually and with small amounts. Periodic spirometry is of great help in such a case; if the vital capacity falls too rapidly after the first

4. Underhill, S. W.: An Investigation into the Circulation of the Lungs, Brit. M. J. **11**:779 (Nov. 12) 1921.

5. Rubow, V.: In Kardiale Dyspnea, Ergebn. d. inn. Med. u. Kinderh. **111**:92, 1909.

insufflations, the quantity of gas introduced with the subsequent refills should be diminished; otherwise, marked dyspnea may ensue.

WHAT IS THE RELATION OF THE ALTERED VITAL CAPACITY AND THE MODIFIED FUNCTION OF THE LUNGS TO DYSPNEA?

A clear distinction between hyperpnea and dyspnea should always be borne in mind. As long as the lungs respond easily and without undue exertion to any urgency for an augmented ventilation, there is merely a hyperpnea, but if the lungs fail to cope with the increased demand for an excessive ventilation, then dyspnea occurs.

Whenever the tidal air becomes insufficient to satisfy the requirements for oxygenation, the complemental air is called on by increasing the depth of inspiration. Peabody [6] attributes the dyspnea of patients with weak or damaged hearts to their inability to increase their inspiration whenever necessary. The same applies to the dyspnea provoked by any diminution of the respiratory surface due to diseases of the pulmonary parenchyma, the degrees of which are determined chiefly by the extent to which pulmonary ventilation is crippled and the depth of the inspiration inhibited. One would therefore expect a marked dyspnea in artificial pneumothorax cases, in which the respiratory surface is always diminished a great deal. Such, however, was not the case. We were amazed to notice that tuberculous patients with a vital capacity of 1,200 c.c. were very dyspneic and could hardly take a few steps without stopping "for air," whereas pneumothorax patients whose vital capacity was the same or even lower were fairly comfortable, and were up and about without showing any signs of respiratory distress. Paradoxic as it may seem, this is probably due to the greater respiratory efficiency of the expansile pneumothorax lung.

Howell [7] states that the new-born child has practically no reserve supply of air in the lungs; at each expiration, the lungs are entirely emptied (except for the minimal air). The ventilation of the lung alveoli is correspondingly more perfect than in older persons. The smaller the residual air, the better is the ventilation of the lungs. It follows, therefore, that in moderately collapsed, not compressed lungs, i.e., in a pneumothorax of the expansile type, the ventilation is better than in physiologically functioning lungs, since, as was indicated previously, the residual air is greatly diminished and all the air coming in with the inspiratory movement goes out with each expiration (except the minimal air) and is entirely renewed. This quantity of air, even if it amounts only to 200 or 300 c.c., is of great value in preventing dyspnea,

6. Peabody, F. W., and Wenworth, J. A.: Clinical Studies of the Respiration, Arch. Int. Med. **20**:442 (Sept.) 1917.

7. Howell, W. H.: Textbook of Physiology, Philadelphia, W. B. Saunders Company, 1918, p. 654.

because the physiologic tidal air, i.e., the new air breathed in at each ordinary inspiration amounts to only 500 c.c.; but, as the "dead space" occupies about 150 c.c., it follows that the ventilation of the lung in normal respiration is only 350 c.c. At each inspiration, therefore, only 350 c.c. of air penetrates into the alveoli; and, since the reserve supply of the lung may amount to 2,600 c.c. (supplemental air 1,600 c.c. and residual air 1,000 c.c.), it follows that the "ventilation volume" of the alveoli is only $^{350}/_{2,600}$, or about one-seventh. But, in expansile pneumothorax, in which all the surface is reduced and the reserve supply is diminished, the "ventilation volume" of each alveolus is much more effective. Another reason for a better ventilation in the expansile pneumothorax lung is the greater volume of blood that runs during the same unit of time through the collapsed lung; i.e., the same amount of blood flows through a reduced area, as was discussed previously. This acceleration of blood flow through the pulmonary capillaries brings about a more rapid absorption of carbon dioxid from the alveoli, which in turn provokes a more rapid diffusion of the new air breathed in at each inspiration and, hence, a more effective oxygenation.

Of course, in cases of completely compressed lungs, there can be no question of tidal air and reserve air, because such lungs take almost no part in the process of ventilation. Patients treated with compression pneumothorax become very dyspneic and remain so for a long time, unless the other lung compensates well and adapts itself to its new task of performing an almost doubled respiratory function. This vicarious adjustment of the contralateral lung commensurates with the compensatory capacity of the heart, particularly of the right ventricle, which has to propel the blood against an increased resistance; if the cardiac muscle has been damaged by the long continued tuberculous toxemia and its reserve power has been weakened, venous stasis of the lung usually ensues, which entails poor oxygenation and consequently is attended by greater dyspnea.

The relation of dyspnea to the diminution of the vital capacity in expansile pneumothorax and in compression pneumothorax is illustrated in the following two cases:

One patient was given pneumothorax because of a protracted febrile course, unaffected by sanatorium treatment, and the other one, on account of frequently repeated and copious hemoptysis. The first patient was given small amounts of gas, and his intrapleural pressure was kept negative all the time; the vital capacity was reduced 10 per cent. the first day, and it was never decreased to more than four-fifths of what it was before the initiation of pneumothorax. He was dyspneic only the first few hours after induction of pneumothorax, but the next day came to the operating room without exertion, and none of the subsequent reinsufflations were attended by dyspnea. The other case was given large amounts of gas and a positive intrapleural pressure was created in order to afford an effective ligation of the bleeding blood vessels; his vital capacity was reduced about 45 per cent.; he could hardly take a few steps without support, and remained dyspneic for a long period of time.

CLINICAL AND PROGNOSTIC SIGNIFICANCE OF PERIODIC SPIROMETRY IN PNEUMOTHORAX THERAPY

A variable series of vital capacity changes are observed, during the long course of artificial pneumothorax, in accordance with the manifold pathologic and functional modifications that necessarily take place throughout the evolution of the collapse therapy. These spirometric readings, if studied carefully and interpreted properly in conjunction with the physical signs and roentgenologic findings, afford a great deal of information as to the status of the collapsed and contralateral lungs, particularly of their respiratory capacity and functional recuperation. Indeed, whereas the symptomatology is indicative more or less of the activity of the lesion, and the roentgenography betrays the anatomic-pathologic changes of the lung, spirometry is the only means by which we measure the recuperation and compensation of the physiologic function of the lung, and is of great help in prognosticating the success or failure of the therapy.

After the initial injection of gas into the pleural cavity, there is always a fall in the vital capacity corresponding to or exceeding the amount of air introduced, this being due not only to the actual reduction of the respiratory surface, but also to the altered intrathoracic pressures to which the circulatory and the respiratory systems are trying to adjust themselves, bringing the hemodynamics and the pneumodynamics to a new equilibrium. The decreased ventilation of the lungs and the deoxygenation is made up for by the tachypnea which is marked the first few hours after the initiation of pneumothorax. The rate of breathing, however, soon resumes its former limit and the vital capacity increases slightly though it still remains below what it was prior to the initiation of the treatment. But, if the initial pneumothorax entails a decrease of more than 15 per cent. of the respiratory capacity, dyspnea ensues, and the patient feels very uncomfortable. The initiatory amount of gas introduced into the pleural cavity should therefore never be greater than one-sixth of the vital capacity of the patient; the smaller the quantity the less the disturbance in the respiratory and circulatory system. If the vital capacity, for instance, is 3,000 c.c., about 400 c.c. of air is to be given at the initial pneumothorax; if the vital capacity is only 2,000 c.c., not more than 300 c.c. of air is advisable for the first injection. The few, immediate subsequent insufflations should also be commensurate, in the same way, with the vital capacity of the patient.

In rare cases, the vital capacity increases after induction of pneumothorax, if the amount of gas injected was small. These are patients who had severe pleuritic pains, inhibiting any attempt at deep breathing; but, now that a thin layer of air separates the visceral from the parietal pleura, the deepest inspiratory movement can be accomplished, provided the

heart is in good condition and there is no great alteration in the intrathoracic equilibrium. In other cases, there occurs no change at all in the vital capacity after induction of pneumothorax. These are patients with marked pleural synechiae, leading to the formation of a small localized pneumothorax, leaving the rest of the lung unaffected. The vital capacity of such cases shows no further modification incidental to the pneumothorax, and, as a rule, these cases benefit very little by the treatment.

The immediate reinsufflations, which are spaced at intervals of two or three days, cause a further diminution of the vital capacity, which is very gradual and persistent. Should a sudden drop occur in the vital capacity during this time, a careful examination of all the factors affecting it is to be made, physically and roentgenoscopically, and the subsequent refills will be modified accordingly. A spontaneous pneumothorax might develop and, with the exception of a transient dyspnea, cause no symptoms at all if a rigid mediastinum that holds off the pressure from the contralateral lung exists, and the heart has, by this time, compensated sufficiently to be able to propel the blood against the increased resistance. But the vital capacity is greatly reduced, and dyspnea, on exertion, is inevitable. No refills should be made into such a pneumothoracic cavity, as it may lead to a complete compression of the lung and consequently to a permanent decrease of the respiratory capacity, but the patient should be made to blow the spirometer every day in order to achieve an expansion of the nondiseased alveoli and return to the former vital capacity. If the spontaneous pneumothorax is distressing, air should be aspirated from the pleural cavity until negative intrathoracic pressure is reached, which allows the lung to dilate with each inspiratory movement, and, of course, the vital capacity is at once elevated.

When no complications occur and the deflation of the lung is graduated slowly and systematically, then the functional modifications of the respiratory capacity are very characteristic, as studied by the "preinsufflatory" and "postinsufflatory" spirometric readings.

A steady step by step decline of the vital capacity is noticed with each insufflation, the cumulative effect of which results in a marked curtailment of the respiratory capacity, but with no distress to the patient, who has little by little adjusted himself to this gradually modified ventilation of the lung. However, a limit is reached which may be looked on as the turning point in the evolution of the collapse therapy when the vital capacity beings to ascend gradually or remains stationary for a time and then increases very slowly but persistently. This transitory point of the vital capacity, in the long course of artificial pneumothorax, is of great value in prognosticating the ultimate result of the therapy, provided no complications set in. It varies with each case in time and amount; it may take place at any time during the course of the treatment and at

any level below the physiologic vital capacity for that person. If it occurs between the first and fourth month after the initiation of the treatment and if the vital capacity at that period is not below 70 per cent. of the physiologic vital capacity for that person, the prognosis is very good. Even when the vital capacity is below 70 per cent. but remains stationary or increases gradually without marked fluctuations, the prognosis is also favorable.

A stationary vital capacity, regardless of whether it is high or low, always signifies that the lesion became arrested or quiescent. In a large group of cases not treated with artificial pneumothorax, we found that the same lesion, when it became active, was liable to reduce the vital capacity to about half its original amount, and therefore those who had a labile lesion exhibited marked fluctuations in their serial spirometric measurements, whereas those who had a quiescent lesion showed either an increasing or a persistently stationary vital capacity. Marked fluctuations in the vital capacity always meant an active lesion. The same holds true in the cases treated with artificial pneumothorax. When the vital capacity becomes stationary or begins to increase very gradually but persistently, it indicates that the diseased areas have become compressed and quiescent, ceasing to discharge toxins into the system, that a complete equilibrium has been established in the respiratory system, and that not only the contralateral lung has developed compensatory emphysema, but also that the functioning portion of the homolateral lung is adjusting itself to its modified way of functioning and is able to develop a vicarious emphysema to expand and occupy the spaces of the hemithorax left empty by the contracted diseased parts of the lung. It is this gradual but steady enlargement of the expansion that brings about the slowly progressive increase in the respiratory capacity, provided no complications arise.

Two phenomena are thus taking place simultaneously as far as the treated lung is concerned: The diseased portion contracts and shrinks continually, while the uninvolved portion keeps on dilating progressively. This should be borne clearly in mind whenever reinsufflations are made. These inflations are not given with the purpose of "knocking the entire lung out of commission," but to assist in keeping the diseased parts in their compressed and contracted position, allowing at the same time the uninvolved portions of the lung to expand and contract more or less freely with each respiratory movement. The amount of air introduced now into the pleural cavity should never curtail more than half its own quantity of the vital capacity, and as we progress successfully in the course of the treatment, the curtailment should be diminished correspondingly, and the introduced volume of air should bring about a reduction in the vital capacity amounting to less than one-fourth its volume. The reasons have been discussed fully in the previous chapters.

Suffice it to mention here again that, all the other factors being equal, it depends wholly on the degree of expansion of the uninvolved portion of the lung; the greater the expansion, the more air is breathed during inspiration, and the more air can be expelled during expiration, consequently, the greater increase in the vital capacity. Of course, this holds true only when moderate amounts of air are administered. If, however, a large quantity of air is introduced, it encroaches also on the functioning tissue, and naturally a great reduction in the vital capacity ensues. It is therefore advisable to inject always about the same amount at the same intervals of time, and note the difference between the preinsufflatory and the postinsufflatory vital capacity, which should become smaller as we advance in the treatment. Each case should be studied roentgenoscopically before and after every inflation, the expansile capacity of the undiseased portion of the lung observed closely, frequent physical examinations of the chest made, all these findings corroborated with the serial spirometric readings, and the insufflations modified accordingly.

If fluid develops, the drop in the vital capacity may be very marked and sudden, both because of an actual reduction of the respiratory capacity and because of pyrexia, probable toxemia and increased strain on the heart preventing the taking of a deep breath. Fluid should never be left in the chest for a long time, as it is liable to cause a permanent injury to the expansion of the lung tissue. It should be aspirated as soon as possible and replaced partially by air, which is managed much more easily, is absorbed more quickly, and allows the undiseased tissue to expand. If not much injury has been done to the elastic quality of the tissue, it will show itself immediately after the aspiration of the fluid by an increase in the vital capacity. The volume of air replaced should always be less than the amount of fluid aspirated. The patient should blow the spirometer every day from three to five times; the gradual increase in the vital capacity should be noted, then treated as a usual case of expansile pneumothorax.

No untoward results come from frequent blowing of the spirometer, even during the first few weeks of the treatment, though, as a rule, we do not let patients blow more often than before and after each insufflation. But as soon as the patient becomes more or less symptomless, expectoration is brought to a minimum and all signs indicate that the lesion has become quiescent, we let the patient take the vital capacity very frequently, first, in order to have a serial record and, second, to enable the expansile portion to dilate more and more. This displaces the gas into spaces left by the compressed, diseased parts of the lung and thus compresses them more. The expansile phenomenon is displayed in such cases most vividly. If not interfered with by improper treatment and complications, these functioning lobes reexpand finally to their full capacity, and, owing to the compensatory emphysema developed in them,

their functional recuperation is very marked. The vital capacity of such cases is greater than what it was prior to the initiation of pneumothorax, and, in two of our cases, the vital capacity came up to more than a 100 per cent. of the calculated physiologic vital capacity for these patients.

It should be emphasized again that all serial spirometric changes described above accompany only cases treated with expansile pneumothorax, but if compression pneumothorax is instituted and maintained, no recuperation of the functional capacity can be expected. We seldom treat with compression pneumothorax now; only, in case of severe hemoptysis, we create a highly positive intrapleural pressure in order to effect a better ligation of the bleeding blood vessels, but even in such cases we soon allow the expansibility of the undiseased portion to assert itself. Of course, when fibrosis preponderates all over the lung, no reexpansion can be expected, and, once compressed, the lung will remain so forever, requiring refills every now and then to prevent deformity of the chest. The vital capacity of such patients is always at a very low level and can never be increased. This might be used as the strongest argument in favor of initiating pneumothorax in early cases and not waiting till the patient and the lung have lost their recuperative ability. At that time, pneumothorax can offer only ameliorative results, whereas, if it is administered to patients in the first or in the second stage of pulmonary tuberculosis, complete anatomic and functional recovery can be expected.

In a later contribution on the results of artificial pneumothorax, there will be discussed fully the relation of age, sex, side of pneumothorax, and involvement of the contralateral lung to the anatomic and particularly to the functional recovery. Suffice it to mention here that we found that the recuperation of the functional ability of the lung and return to their physiologic vital capacity was more frequent in young persons than in old ones, owing, no doubt, to the better reserve power of their hearts and the more pronounced elastic quality of their lung tissues, enabling the development of a marked compensatory emphysema.

The vital capacity percentage of the subject before the initiation of the pneumothorax also has a great bearing on the ultimate result of the treatment. Those patients whose vital capacity is not much below their calculated physiologic normal do, as a rule, much better than those who have a low vital capacity, and if the expansile pneumothorax is managed properly and graduated systematically, the pulmonary function recuperates slowly but persistently, and the lungs may eventually attain their complete physiologic respiratory capacity.

SUMMARY AND CONCLUSIONS

1. The vital capacity modifications during the course of artificial pneumothorax treatment are very characteristic, and careful periodic

spirometry can therefore afford a great deal of information about the respiratory recuperation of the lungs and how to regulate the insufflatory amounts, and can be used as an additional criterion in prognosticating the success or failure of the therapy.

2. There is no quantitative correspondence between the amount of air introduced into the pleural cavity and the reduction of the vital capacity, but the same quantity of air at various inflations brings about different results depending on the status of the other factors modifying the vital capacity in pneumothorax, the most important of which are:

(*a*) The residual air of the collapsed lung which, owing to the increased expiratory intrapleural pressure created in the treated hemithorax, is expelled with each deep expiration and thus made to participate in the vital capacity.

(*b*) The newly established intrapleural pressures which antagonize each other as far as the vital capacity is concerned: a high inspiratory pressure entails a diminution in the complemental air, thus reducing the vital capacity, whereas a high expiratory pressure augments the supplemental air, which means an increase in the vital capacity.

(*c*) The extent of the pathologic involvement and the functional ability of the treated lung which depends on the elastic quality of the tissue; the greater the injury to the *expansibility* of its elastic tissue, the greater and more permanent is the decrease in the vital capacity.

(*d*) The mediastinum which, if rigid, has little effect on the vital capacity, but, if labile, encroaches on the contralateral lung when a high intrapleural pressure exists and causes a diminution in the vital capacity.

(*e*) The heart, when weakened by the continuous tuberculous toxemia, may fail to meet the demand for additional work in propelling the same amount of blood against an increased resistance in the pulmonary circulation; venous stasis and turgescence of the lung blood vessels follow, leading to a diminution in the vital capacity. The demand on the reserve power of the heart stands in direct relation with the degree of deflation of the lung.

3. Patients with a low capacity who are treated with pneumothorax have much less dyspnea than other tuberculous patients having the same low vital capacity, this being due to the residual air of the treated lung which is also breathed out and renewed with each increased respiratory movement, rendering the "ventilation volume" of each alveolus much more effective. If, however, the introduced air into the pleural cavity curtails more than one fifth of the vital capacity of the patient, dyspnea ensues.

4. There are three distinct phases in the vital capacity during the course of the treatment: a gradual decrease, a stationary period, and slowly progressive increase. If the initial decrease is sudden and marked,

in spite of the small amount of air injected at each insufflation, the prognosis is not very favorable. A stationary vital capacity, even at a low level, is much better than high vital capacity showing marked fluctuations, which always signifies a labile lesion. The earlier the starting point of increase in the spirometric readings is noticed and the higher the level of the vital capacity at which it starts, the better is the prognosis for a complete respiratory recuperation.

5. The difference between the preinsufflatory and the postinsufflatory vital capacity corresponds to the amount of air introduced into the pleural cavity only at the commencement of the treatment, but, as we advance in the course of the treatment and the expansibility of the uninvolved portion of the lung begins to assert itself, the difference becomes smaller and may amount to less than one fourth of the quantity of air introduced, provided the inspiratory intrapleural pressure is left negative, allowing the functioning portion to dilate to its full capacity.

6. No larger amount than one sixth of the vital capacity of the patient should be administered at the initiation of the pneumothorax. The amounts of the subsequent inflations should also commensurate in the same way with the vital capacity, but, in accordance with differences in the preinsufflatory and postinsufflatory spirometric readings, which are constantly changing throughout the course of the treatment.

7. Those who have a high vital capacity before the initiation of the treatment, as well as patients with anatomic lesions of the first or second stage, and particularly young people show a much better respiratory recuperation of the lung than other patients do, and, if properly managed and no complications set in, may attain their full physiologic vital capacity.

8. The long series of spirometric modifications as well as the complete recuperation of the respiratory capacity of the lung is observed only in cases treated with expansile pneumothorax, but in compression pneumothorax, in which the respiratory function of the treated lung is reduced to its minimum, the vital capacity diminution is very marked, and may remain permanently at its low level if fibrosis and atelectasis preponderate in the compressed lung, which is unable to reexpand. A small localized pneumothorax, because of strong pleural adhesions, has hardly any effect on the vital capacity.

9. Fluid should be aspirated as soon as possible from the pleural cavity to avoid permanent reduction of the respiratory capacity, should be partially replaced by air, and the patient made to blow the spirometer a few times daily. This effects a gradual reexpansion of the atelectatic lung and a progressively increasing vital capacity. No untoward results have been noticed in any of the patients from frequent blowing of the spirometer.

DREYER'S TUBERCLE ANTIGEN

EXPERIMENTS SHOWING THE FAILURE OF THE ANTIGEN TO PROTECT GUINEA-PIGS AGAINST EXPERIMENTAL TUBERCULOSIS *

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The experiments herein reported were undertaken as a preliminary investigation of the problem of the possible efficacy of Dreyer's tubercle antigen in the treatment of guinea-pigs infected with tuberculosis. It was planned to continue the experiments on a larger scale, using a much greater number of animals inoculated with material of varying grades of infectivity, and employing an adequate series of controls. The result of this preliminary study was so discouraging, however, that it was not felt that the labor and expense of an elaborate investigation would be justified. Dreyer's paper attracted considerable attention and yet there has been a great paucity of either confirmatory or contradictory reports by other workers; because of this it was felt that our negative results should be recorded.

Dreyer,[1] in 1923, asserted that, as a general rule, most of the failures in vaccine therapy have been with the acid-fast and the gram-positive organisms. Since acid-fastness and gram-positiveness have been associated with the presence in the bacterium of certain waxy, fatty or lipoid substances, it would seem quite probable that the latter prevent the escape of the antigen from the organism and thus block the sole adequate stimulus for the immunity reaction. Therefore, Dreyer devised a method for removing the lipoidal substance from the tubercle bacillus and rendering the organism nonacid-fast. Tubercle bacilli grown on glycerin broth are treated repeatedly with formaldehyd and then extracted several times with acetone in a Soxhlet apparatus. The insoluble residue is dried and ground, and the organisms are tested as to their acid-fastness. If this quality persists, it is necessary to repeat the entire procedure. Often this must be done three or four times before the bacilli become nonacid-fast. This method involves rough handling of the organisms, and it might be thought that their

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1. Dreyer, G.: Some New Principles in Bacterial Immunity; Their Experimental Foundation, and Their Application to the Treatment of Refractory Conditions, Brit. J. Exper. Pathol. **4**:146 (June) 1923.

chemical make-up is thereby seriously altered. On subjecting *Bacillus typhosus* to the same process, however, Dreyer found that this organism was still able to cause the production of immune substances. With the nonacid-fast tubercle bacilli produced by this process, termed "defatted" antigen or "diaplyte" antigen, Dreyer reported that he was enabled to produce specific precipitins, agglutinins and complement fixing bodies in normal rabbits.

With a view to study the therapeutic effects of his defatted tubercle antigen on animals suffering from well defined tuberculosis, Dreyer treated four infected guinea-pigs, three of them being the sole survivors of a group of twenty-five animals that had been inoculated with a strain of human tubercle bacilli that had caused death in the other twenty-two animals in from four to ten months. It must be borne in mind that this procedure gave Dreyer the most resistant guinea-pigs in the lot; hence, the twenty-two animals that had died cannot be considered as controls. The experiment was performed on selected animals that had already manifested a relative degree of resistance to tuberculosis, and there were no real controls.

At the time when treatment was begun, all Dreyer's animals showed well marked evidences of tuberculosis. At the date of Dreyer's report, the first guinea-pig, forty-eight weeks after infection and twenty weeks after treatment was begun, was of normal weight for its age, and the inguinal glands were smaller and harder than they had been. The second animal, whose date of infection was not recorded, appeared healthy sixteen weeks after commencement of treatment, and the inguinal glands had disappeared. The third guinea-pig, fifty-five weeks after inoculation and sixteen weeks after treatment was begun, appeared improved, but was underweight and suffered from a diarrhea. The fourth animal, fifty weeks after infection and eleven weeks after treatment was begun, gave birth to young and died a few days later. At necropsy, there was a generalized tuberculosis, but all the lesions showed abundant fibrosis, with the presence of giant cells and an absence of the lymphocytic reaction seen in active tuberculosis. Dreyer believed that the histologic picture was such as to indicate a tendency to heal. From these experiments, he concluded that treatment with diaplyte antigen brings about a definite improvement, both general and local, in animals infected with *B. tuberculosis*.

As demonstrated by Baldwin and Gardner,[2] it is necessary to observe guinea-pigs infected with tuberculosis over long periods of time before passing judgment as to ultimate recovery. Often a very sleek, well nourished animal appears to have recovered after from six to eight months,

2. Baldwin, E. R., and Gardner, L. U.: Reinfection in Tuberculosis: Experimental Arrested Tuberculosis and Subsequent Infections, Am. Rev. Tuberc. **5**:429 (Aug.) 1921.

only to emaciate gradually, lose his perirenal fat, develop dyspnea from gradual consolidation of the lungs, and finally die from the disease or some complication. Some of our animals died suddenly, while fat, from hemorrhage due to erosion of a large vessel by tubercles.

Krause,[3] in 1919, reported experiments with a strain of tubercle bacillus, long cultivated under artificial conditions, which was so avirulent that guinea-pigs successfully overcame infection by inhalation of it. Such an organism produced a caseous reaction, but, instead of spreading from the initial foci, the process slowly underwent retrogressive changes and, in some instances, finally completely disappeared. Dreyer's guinea-pigs were infected with an organism of slight virulence, which had not passed through an animal for fifteen years.

So far as the authors have been able to ascertain, there have thus far been reported no experiments relating to the treatment of tuberculous guinea-pigs with Dreyer's antigen, with the exception of Kettle's [4] observations and Caulfield's [5] recent article. Kettle, in his experiments on guinea-pigs, was unable to demonstrate any curative action of Dreyer's antigen. In fact, there was much evidence to suggest that the antigen had an adverse action on the guinea-pig treated with it, even in comparison with bacillary emulsion.

Caulfield treated six tuberculous guinea-pigs with weekly injections of 0.5 c.c. (0.1 mg. of dried bacilli) of Dreyer's antigen and gave four additional animals both prophylactic and therapeutic injections. There were four controls. All fourteen animals died of generalized tuberculosis. The average length of life in the controls was ten and a half weeks; in the treated guinea-pigs, ten weeks; in the animals receiving both prophylaxis and treatment, thirteen and seven-tenths weeks.

AUTHORS' EXPERIMENT

The antigen used by us, in this experiment, was prepared strictly in accordance with Dreyer's technic from the Board of Health Strain 305 of human tubercle bacilli, grown on glycerin broth. This was known to be an organism of medium virulence. We were able to verify the fact that the process described by Dreyer renders tubercle bacilli nonacid-fast, although it was necessary to subject the organisms four times to formaldehyd action and acetone extraction in order to bring about this result.

3. Krause, A. K.: Studies on Tuberculous Infection, I, A Note on Experimental Tracheobronchial Node Tuberculosis Together with a Brief Consideration of Several Phases of Tuberculous Infection Suggested Thereby, Am. Rev. Tuberc. **3**:1 (March) 1919.

4. Kettle, E. H.: The Criteria of Cure in Tuberculosis of the Guinea-Pig with Special Reference to Diaplyte Antigens, Lancet **1**:68 (Jan. 12) 1924.

5. Caulfield, A. H. W.: A Preliminary Report on the Clinical and Experimental Use of Dreyer's Tuberculoantigen, Canad. M. A. J. **14**:616 (July) 1924.

Our initial dosage was only one-fourth that employed by Dreyer, that is we used 0.025 mg. of dried tubercle bacilli instead of 0.1 mg. Later in the experiment, however, we ran the dosage up to the 0.2 mg. employed by Dreyer. Moreover, vaccine treatment was begun much earlier in the course of the disease, usually before the appearance of glandular enlargement; in nine of the guinea-pigs, from one to three vaccine injections were made before infection. The smaller dosage was used with the idea that the antigen might prove to be toxic to the

Effect of Dreyer's Antigen on the Course of Experimental Tuberculosis in Twenty-One Guinea-Pigs, with Four Controls

	Guinea-Pig	Date of Inoculation	Date of Starting Treatment	Number of Injections	First Appearance of Glandular Enlargement (Days After Infection)	Length of Life After Infection (In Weeks)
Group 1: Eight healthy young guinea-pigs (including two controls) inoculated subcutaneously in right thigh with 0.1 mg. of Board of Health Strain 305 of human tubercle bacilli	7	9/14/23	10/23/23	17	12*	28
	24	9/14/23	10/23/23	17	17*	39
	26	9/14/23	10/23/23	10	17*	18
	19	9/14/23	9/23/23	16	12	21
	18	9/14/23	9/23/23	22	12	36
	40	9/14/23	9/23/23	16	12	21
(Control)	15	9/14/23	.....	..	15	17
(Control)	49	9/14/23	.....	..	15	26
Group 2: Eleven healthy young guinea-pigs (including one control) inoculated subcutaneously in right thigh with 0.01 mg. of culture "Maisola" (from sputum of active case of pulmonary tuberculosis) of human tubercle bacilli	31	9/29/23	9/22/23	16	..	17
	6	9/29/23	9/22/23	16	..	24
	23	9/29/23	9/22/23	20	..	24
	41	10/ 5/23	9/22/23	20	..	24
	35	10/ 5/23	9/22/23	16	..	16
	45	10/ 5/23	9/22/23	11	..	10
	158	10/ 5/23	10/23/23	12	..	18
	50	10/ 5/23	10/23/23	15	..	23
	388	10/ 5/23	10/23/23	15	..	22
	220	10/ 5/23	10/23/23	12	..	18
(Control)	30	9/29/23	.....	..	..	19
Group 3: Six healthy young guinea-pigs (including one control) inoculated subcutaneously in right thigh with 0.01 mg. of culture "Ravenol" of virulent bovine tubercle bacilli	8	10/5/23	9/22/23	10	..	8
	9	10/5/23	9/22/23	10	..	8
	47	10/5/23	9/22/23	10	..	8
	36	10/5/23	10/23/23	4	..	6
	20	10/5/23	10/23/23	4	..	7
(Control)	10	10/5/23	.....	..	..	7

All the guinea-pigs, both treated and controls, died of generalized tuberculosis. The initial dosage was 0.025 mg., the maximum dosage, 0.2 mg. (in terms of mass of dried tubercle bacilli).

* Glandular enlargement appeared before antigen treatment was started. In the three treated animals, adenopathy appeared earlier than in the five controls.

animals, and that it would be to their advantage to start early with small amounts, which would be gradually increased. This procedure seemed justified by subsequent developments, in that there was earlier adenopathy in the treated animals and a more rapid loss of weight in the guinea-pigs receiving full doses.

The vaccine was injected into the subcutaneous tissue of the abdomen. Injections were made weekly; on several occasions, two weeks were allowed to elapse. Two doses each of 0.025 mg., then five doses of 0.05 mg., then six doses of 0.1 mg., then three doses of 0.2 mg. were given. The remaining doses were of 0.1 mg.

The salient features of the experiment are indicated in the accompanying table. Twenty-five guinea-pigs, weighing between 280 and 400 gm., were inoculated with living tubercle bacilli, of which group twenty-one were treated with the antigen, four serving as controls. In nine instances, vaccination was begun before the animals were inoculated. The animals of Group 1, comprising six treated guinea-pigs and two controls, were inoculated subcutaneously in the right thigh with 0.1 mg. of Board of Health Strain 305 of human tubercle bacilli. Those of Group 2, comprising ten treated animals and one control, were infected with 0.01 mg. of a strain of human tubercle bacilli cultured by us from a patient with active pulmonary tuberculosis. The animals of Group 3, comprising five treated guinea-pigs and one control, were inoculated with 0.01 mg. of a culture of virulent bovine tubercle bacilli. The animals were weighed at frequent intervals, but as their weight curves do not add much of interest, we have dropped such data from the tabulation. We found, as did Dreyer, that the larger doses of vaccine (0.2 mg.) often caused rapid loss of weight from which the animal would recover if treatment was suspended for a couple of weeks.

All the twenty-five animals employed in this experiment died with postmortem evidences of generalized tuberculosis, and there was no apparent difference in the course of the disease between the treated animals and the controls. As a matter of fact, two conditions observed would indicate that the antigen is in itself either toxic or sensitizing: (1) There was a tendency for earlier glandular enlargement in the treated guinea-pigs, and (2) cessation of vaccine treatment in emaciated animals would often be followed by considerable gains in weight. By referring to Group 1 of the table, it will be noted that in the three starred animals glandular enlargement appeared before vaccine treatment was begun. If we take these three animals, together with the two which at no time received treatment, as controls, it will be observed that adenopathy appeared earlier in the vaccinated than in the untreated animals.

CONCLUSION

A study of the course of the disease in a group of twenty-five guinea-pigs experimentally infected with tuberculosis, of which group twelve received therapeutic vaccination with Dreyer's tubercle antigen and nine both prophylactic and therapeutic vaccination, four animals serving as controls, failed to adduce any evidence that this antigen protects guinea-pigs against tuberculosis, prolongs life, or in any way favorably influences the course of the disease.

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INULIN AND ARTICHOKES IN THE TREATMENT OF DIABETES *

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INTRODUCTION

The use of Jerusalem artichokes, the edible vegetable in which inulin is most commonly found, in the diabetic diet has interested students of the disease ever since Külz [1] and Bouchardat [2] recommended it. Külz and Bouchardat believed that inulin was utilized better than starch, but von Noorden [3] stated that this would not hold true with the severe cases in the same degree as with the mild ones. Sandmeyer,[4] Persia,[5] Lewis [6] and Goudberg [7] noted that inulin, when fed by mouth, appeared either not at all or in small amounts in the stools in the normal man. Sandmeyer, however, recovered in the stools more than half the inulin given to a dog, whose pancreas had been removed. Goudberg, who reviewed the subject exhaustively, gave from 100 to 200 gm. of inulin to diabetic subjects, and observed a pronounced rise in the respiratory quotient and in the metabolism, persisting for from six to ten hours afterward in some cases. He therefore concluded that it was well utilized. Offenbacher and Eliassow [8] and Dumont [9] also found inulin in the form of artichokes useful in the diabetic diet. Mendel,[10] however, was unable to find any ferment or enzymes in the body which would hydrolyze the inulin, and therefore held that the good results of inulin feeding were

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* From the Diabetic Clinic of the New England Deaconess Hospital.

* This paper is No. 46 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

1. Külz: Beitr. z. Path. u. Therap. der Diabetes, Jahrb. Tierchem. **4**:448, 1874.

2. Bouchardat, quoted by von Noorden, in Von Leyden's Handbuch des Ernahrungs Therapie **2**:227, 1904.

3. Von Noorden (Footnote 2).

4. Sandmeyer, W.: Ztschr. f. Biol. **31**:32, 1895.

5. Persia: Nuova Rivista Clin. Therapeut **8**, 1905; Jahrb. Tierchem. **25**:822, 1905.

6. Lewis, H. B.: The Value of Inulin as a Foodstuff, J. A. M. A. **58**:1176 (April 20) 1912.

7. Goudberg: Ztschr. f. exper. Path. u. Therap. **13**:310, 1913.

8. Offenbacher, R., and Eliassow, W.: München. med. Wchnschr. **69**:1508 (Oct. 27) 1922.

9. Dumont: Bull. Acad. de méd. **87**:721 (June 27) 1922.

10. Mendel, L. B.: Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs. **3**: 641, 1908.

due to its nonabsorption. Lewis,[6] Chittenden,[11] Bierry[12] and others recognized that hydrolysis of inulin by the hydrochloric acid of the stomach would liberate some levulose. Neubauer[13] found no increase in the excretion of levulose in a case of levulosuria after the giving of inulin, and Lewis and Frankel[14] obtained no increase in glycosuria in phloridzinized animals after inulin feeding. The recent studies of Okey[15] have thrown new light on the behavior of inulin, as she has shown that not only is inulin hydrolyzed by the hydrochloric acid of the stomach but also that an inulase may be isolated from the feces of normal subjects. The nature and source of this inulase is not explained. It may be of bacterial origin, such as occurs in *Penicillium glaucum* and *Aspergillus niger*. The latter has been studied by Grafe and Vouk.[16] Green,[17] Bourquelot[18] and Dean[19] have found inulase in various plants. Green states that the enzyme inulase occurs only in the germinating tuber. In the resting tuber, the enzyme occurs as a zymogen from which it may be released by the action of "warmth" or under conditions of mild acidity. The enzyme hydrolyzes inulin very slowly, some of his experiments extending over a period of six days. It is completely destroyed by boiling and by the action of 0.21 per cent. hydrochloric acid at 40 C.

The chemical nature of inulin has been the subject of many investigations. Dean[20] and Willaman[21] regard inulin as a mixture of anhydrids of levulose of varying sized molecules. In artichoke tubers, a series of inulin-like substances (such as inuloids and inulids), different in solubilities but all anhydrids of levulose, is found, some of which may be more easily hydrolyzed than others. True inulin is defined by Dean as the carbohydrate mixture precipitated in cold alcohol of 60 per cent. and with a specific rotation of $[a]\ d = -30°$ to $-40°$. Colin[22] has studied the occurrence of inulin in the tuber of the Jerusalem artichoke, and finds that the leaves elaborate reducing sugars which are condensed in the stem to inulin and stored in the tubers. During the winter months, inulin is converted back into reducing sugars and intermediate products are formed which are more and more readily hydrolized as this transformation proceeds. Thus, in the Jerusalem arti-

11. Chittenden, R. H.: Am. J. Physiol. **2**:17, 1898.
12. Bierry, H.: Compt. rend. Acad. d. sc. **150**:116, 1910; Compt. rend. Soc. de biol. **59**:256, 1905; Biochem. Ztschr. **44**:402, 1912.
13. Neubauer: München. med. Wchnschr., 1905, p. 1525.
14. Lewis and Frankel: J. Biol. Chem. **17**:365, 1914.
15. Okey, R.: J. Biol. Chem. **38**:33 (May) 1919; ibid. **39**:149, 1919.
16. Grafe and Vouk, V.: Ztschr. Garungsphysiol. **3**:327, 1913.
17. Green: Ann. Botany **1**:223, 1888.
18. Bourquelot: Compt. rend. Soc. de biol. **116**:1143, 1893.
19. Dean: Botany Gaz. **25**:69, 1903.
20. Dean, A. L.: Am. Chem. J. **32**:69, 1904.
21. Willaman, J. J.: J. Biol. Chem. **51**:275 (March) 1922.
22. Colin, H.: Bull. Ass. Chim. Sucr. Dis. **37**:121, 1919.

chokes, one may expect that a slight decrease in the amount of levulose derived from inulin would occur during storage in the winter. Dr. J. S. Caldwell has suggested that these changes may not occur so readily in artichokes stored under conditions such as to prevent freezing as when they are stored underground. Table 1 gives analyses of Jerusalem artichokes sampled at intervals for nearly three months. The change in sugars other than levulose was, however, very slight, as the table shows. The figures for sugars are those found after hydrolysis of the inulin.

Shohl [23] also has recently analyzed Jerusalem artichokes, finding 15 per cent. carbohydrate content. He found the vitamin water-soluble B present in scant amounts. Desgrez, Bierry and Rathery [24] have recommended the administration of this vitamin with levulose.

TABLE 1.—*Summary of Analyses of Artichokes from River Ridge Farm, Franklin, Pa.*[*]

Date Received	Levulose	Total Solids in Juice	Total Reducing Sugars	Glucose by Iodin	Ratio of Levulose to Total Sugar
Nov. 9, 1923	13.4	....	17.2	4.5	0.778
Nov. 17, 1923	11.7	....	14.7	3.6	0.796
Nov. 27, 1923	11.8	18.6	....	....	.....
Dec. 3, 1923	12.6	18.6	15.4	4.5	0.818
Dec. 20, 1923	12.5	20.0	15.7	4.0	0.794
Jan. 7, 1924	11.2	17.6	13.3	3.6	0.844
Jan. 17, 1924	10.6	18.4	14.4	....	0.732
Jan. 28, 1924	11.5	18.9	14.7	....	0.782
Jan. 31, 1924	10.4	18.6	....	....	.....

[*] The analyses were made at the Bureau of Standards, Department of Commerce, Washington, D. C., and were furnished us by Joseph C. Sibley with the permission of F. A. Brant, acting director, and George K. Burgess, director.

OBJECTS AND METHODS OF THE INVESTIGATION

Results of previous studies have not agreed as to the food value of inulin. Failure to recover inulin in the stools, the well known hydrolysis of inulin by dilute hydrochloric acid and the increase in the respiratory quotient after inulin feeding reported by one observer have been offset by the absence of a demonstrable inulase in the digestive juices. The question of the usefulness of artichokes in the diabetic diet is a subject requiring study from many angles and is not to be answered by experiments with a single type of inulin extracted from plants, although such experiments may be expected to give helpful information. One must bear in mind (1) the possible hydrolysis of inulin in the stomach and in the intestine; (2) the possible occurrence in the artichoke of anhydrids of levulose intermediate between "inulin" and levulose, and of levulose itself; (3) the existence of an inulase in

23. Shohl, A. T.: J. Am. Chem. Soc. **45**:2754, 1923.
24. Desgrez, Bierry and Rathery: Bull. Acad. de méd. **88**:167 (Oct. 31) 1922.

artichokes; (4) the occurrence of small amounts of glucose and sucrose, and (5) the various effects produced by different types of cooking.

Our studies have been both clinical and experimental. They were inspired by the work described above, the investigations on levulose at the Nutrition Laboratory of the Carnegie Institution and in this clinic,[25] and by the beneficial effects observed with artichokes in our own patients. Clinically, we have used Jerusalem artichokes, inulin and levulose, by adding these foods to the diet, by substituting them for other carbohydrate foods in the diet and by replacing inulin with artichokes. We have relied on changes in the respiratory quotient and heat production as the chief evidence of absorption and utilization of carbohydrate ingested. Metabolism experiments have been carried on by giving the patients in the fasting state varying amounts of artichokes, inulin or levulose and observing changes in the respiratory metabolism, blood and urine during the following six hours. The Tissot apparatus with modified Haldane gas analysis apparatus was used. The figures recorded for the respiratory quotient and the heat production represent averages for three consecutive periods of ten minutes. The inulin employed was prepared from dahlia tubers and provided through the courtesy of Dr. J. S. Caldwell of the United States Department of Agriculture, Washington, D. C. It contained 2.5 per cent. reducing sugar, which was almost entirely levulose. The artichokes, helianthus tuberosus albus, were obtained through the courtesy of Joseph C. Sibley of River Ridge Farm, Franklin, Pa.

EFFECT OF A SINGLE PORTION OF ARTICHOKES ON SIX DIABETIC PATIENTS

The changes in metabolism in six diabetic patients who received baked Jerusalem artichokes in the postabsorptive state are shown in Table 2. All were moderately severe cases under treatment with insulin. This was omitted sixteen hours before and during the test. On the day of the experiment, a preliminary basal metabolism of three ten minute periods was used. The artichokes were freshly baked in their skins and served warm with a little salt and 200 c. c. of Kaffee Hag flavored with saccharin. Benedict and Benedict[26] showed that caffein-free coffee given in this manner did not affect the metabolism. It was intended to give 1.5 gm. of carbohydrate per kilogram of body weight, but variations in the patients' appetites made it possible to try doses of varying amounts.

25. Joslin, E. P.: Diabetic Metabolism with High and Low Diets, Carnegie Inst., Washington, Pub. 323, 1923.

26. Benedict, C. G., and Benedict, F. G.: Boston M. & S. J. **188**:849 (May 31) 1923.

TABLE 2.—*Effect of Baked Artichokes on the Metabolism of Six Diabetic Patients* *

Case	Carbohydrate Given: Total, Gm.	Carbohydrate Given: Grams per Kg.	Weight of Patient Above or Below Standard, per Cent.	Variation of Basal Metabolism from Standard (H. & B.), per Cent.		Basal	Half-Hours After Ingestion: 1	2	3	4	5	6	7	8	9	10	11	12
1	77	2.0	—39	—3	Respiratory quotient	0.76	....	0.84†	....	....	0.84	....	....	....	0.88	....	....	0.87
					Calories per 24 hours	1,081	....	1,222	....	....	1,187	....	....	....	1,185	....	..	1,210
					Percentage deviation from basal	....	....	+13	....	....	+10	....	..	....	+10	....	....	+10
2	79	1.4	—7	—9	Respiratory quotient	0.77	....	0.74	....	0.83	....	....	....	0.83	....	....	....	0.82
					Calories per 24 hours	1,420	....	1,586	....	1,540	....	....	....	1,484	....	....	....	1,466
					Percentage deviation from basal	....	....	+12	....	+9	....	....	....	+5	....	....	....	+3
3	37	0.7	—6	+3	Respiratory quotient	0.74	....	0.74	....	0.74	....	....	0.81	....	....	....	....	0.80
					Calories per 24 hours	1,469	....	1,469	....	1,368	....	....	1,435	....	....	....	....	1,390
					Percentage deviation from basal	....	....	±0	....	—4	....	....	+2	....	....	....	....	—1
4	54	10.9	—7	+1	Respiraory quotient	0.76	....	0.75	....	0.77	....	....	0.79	....	....	....	....	0.81
					Calories per 24 hours	1,321	....	1,385	....	1,454	....	....	1,393	....	....	....	....	1,395
					Percentage deviation from basal	....	....	+5	....	+9	....	....	+5	....	....	....	....	+3
5	81	1.5	—10	+10	Respiratory quotient	0.73	....	0.69	....	0.78	....	....	....	0.77	....	....	....	0.76
					Calories per 24 hours	1,473	....	1,502	....	1,637	....	....	....	1,523	....	....	....	1,505
					Percentage deviation from basal	....	....	+8	....	+11	....	....	....	+3	....	....	....	+2
6	53	1.2	—26	+1	Respiratory quotient	0.82‡	....	0.77	....	0.82	....	....	....	0.86	....	....	....	0.94
					Calories per 24 hours	1,301	....	1,324	....	1,324	....	....	....	1,352	....	....	....	1,303
					Percentage deviation from basal	....	....	+1	....	+3	....	....	....	+4	....	....	....	±0

* Since some of these cases will be mentioned in other papers, for purposes of identification their personal case numbers are given: Case 1, Joslin 3092; 2, Joslin 2880; 3, Joslin 3066; 4, Joslin 3728; 5, Joslin 2687; 6, Joslin 1576; 7, Joslin 3565; 8, Joslin 2947; 9, Joslin 3057; 10, normal, J. W.; 11, normal, M. A.; 12, normal, M. M.; 13, Joslin 3129; 14, Joslin 3640; 15, normal, C. F., and 16, Joslin 3194.

† Maximum, 0.88. ‡ Respiratory quotient 0.82 two days before.

The most striking feature observed was a pronounced rise in the respiratory quotient which occurred uniformly and tended to reach its maximum in from two to six hours. Of these patients, in two instances the maximum respiratory quotients were obtained during the sixth hour, and in three cases quotients within 0.01 of the maximum quotient were obtained in the sixth hour. In two cases, the maximum quotients were obtained in the third and fourth hours. The patients whose weight was most below standard exhibited the greatest increases in respiratory quotient. The amount of carbohydrate taken per kilogram of body weight also influenced the rise in respiratory quotient. The average maximal increase in respiratory quotient was 0.076.

The average maximal increase in heat production was 8.5 per cent. This may be compared with an average maximal increase of 17 per cent. after levulose recorded by Joslin [27] in the Carnegie series, and of 10 per cent. in three mild cases shown in Table 201.[28] The increase in heat production was clearly related to the amount of artichokes taken. Thus Cases 1, 2 and 5 (Table 2) received an average of 83.6 gm. of carbohydrate, with a resultant average increase in metabolism of 12 per cent. Cases 3, 4 and 6 received an average of 47 gm. of carbohydrate, with a resultant average maximal increase in metabolism of 5 per cent.

If we compare these results with the effect of levulose alone on the metabolism, it is seen, in Table 3, that the highest quotients after levulose are obtained within two hours after its ingestion. This is even more apparent in Table 201 of Joslin's book,[28] in which, with one exception, all maximal quotients were obtained within the first two hours after the taking of levulose. The slower and more prolonged effect on the respiratory quotient after the artichokes suggests slower liberation of carbohydrates and slower absorption. In one case, Case 1, a comparison is afforded between the results after artichokes and after levulose. Here, in both instances, the rise in quotients persisted throughout the six hours. The average increase in respiratory quotient was 0.098 with artichokes as against 0.025 with levulose. Similarly, the average increase in heat production was 11 per cent. with artichokes and 11 per cent. with levulose. The maximal increase in respiratory quotient was obtained during the second hour with levulose and during the fifth hour with artichokes.

Diabetic subjects whose metabolism is below standard exhibit a greater increase in respiratory quotient after taking levulose than do those with higher basal metabolism. One may say that a diabetic patient

27. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, 1923, p. 543.

28. Joslin (Footnote 27, p. 292).

TABLE 3.—*Effect of Levulose on the Metabolism of Three Diabetic Patients*

Case	Amount Given: Total, Gm.	Amount Given: Grams per Kg.	Weight of Patient Above or Below Standard, per Cent.	Variation of Basal Metabolism from Standard (H. & B.), per Cent.		Basal	Half-Hours After Ingestion: 1	2	3	4	5	6	7	8	9	10	11	12
7	50.6	1.6	—40	—22	Respiratory quotient	0.81	....	0.82	....	0.95	....	0.86	....	....	0.80	....	....	0.84
					Calories per 24 hours	804	....	825	....	953	....	866	....	....	809	....	....	873
					Percentage deviation from basal	....	....	+3	....	+16	....	+13	....	....	+12	....	....	+9
8	87	1.6	—24	—10	Respiratory quotient	0.76	....	0.80*	....	....	0.74	....	....	0.79	....	....	....	0.78
					Calories per 24 hours	1,650	....	1,967	....	....	1,729	....	....	1,490	....	....	....	1,554
					Percentage deviation from basal	....	....	+18	....	....	+4	....	....	−11	....	....	....	−7
1	48	1.2	—39	−3	Respiratory quotient	0.77	....	0.79	....	0.80	....	....	....	0.79	....	....	....	0.80
					Calories per 24 hours	1,650	....	1,172	....	1,237	....	....	....	1,172	....	....	....	1,141
					Percentage deviation from basal	....	....	+10	....	+16	....	....	....	+19	....	....	....	+7

* Maximum for a single period, 0.83.

TABLE 4.—*Effect of Levulose in Repeated Small Doses*

Case	Amount Given per Hour, Gm.	Hours	Weight of Patient Above or Below Standard, per Cent.	Variation of Basal Metabolism from Standard (H. & B.), per Cent.		Basal	Half-Hours After Ingestion: 1	2	3	4	5	6	7	8	9	10	11	12
9	12	6	—19	—1	Respiratory quotient	0.79	....	0.78	....	0.76	....	0.76	....	0.77	....	0.75	....	0.80
					Calories per 24 hours	1,641	....	1,664	....	1,693	....	1,745	....	1,749	....	1,795	....	1,715
					Percentage deviation from basal	....	....	+1	....	+1	....	+6	....	+7	....	+9	....	+5
6	10	5	—26	+0.4	Respiratory quotient	0.82	....	0.79	....	0.87	....	0.82	....	0.83	....	....	....	0.97
					Calories per 24 hours	1,327	....	1,296	....	1,357	....	1,397	....	1,247	....	....	....	1,364
					Percentage deviation from basal	....	....	−2	....	+1	....	−5	....	−6	....	....	....	+3

must have a subnormal metabolism in order to react to levulose like a normal subject.

Another comparison between levulose and artichokes is presented in Table 4, which gives the effect on the metabolism of levulose in repeated small doses. These two subjects received levulose, in one instance at the rate of 10 gm. an hour, and in the other instance, 12 gm. an hour. Case 9 was a young man, aged 19, with fairly severe diabetes, who did not utilize levulose well. Case 6 is of special interest because results are at hand both after a single administration of artichokes and after levulose given in repeated doses. He had a mild case and utilized both the levulose and artichokes very well. In each experiment, the maximal respiratory quotients were obtained at the end of the six hours. The increases in heat production were greater in Case 9, although in this case there was less increase in respiratory quotient. The curves in blood sugars differed. In Table 6, it is seen that the blood sugar percentages rose steadily during the six hours during which levulose was given, whereas, after the single dose of artichokes, the blood sugars rose to a maximum at the end of two hours and decreased at the end of six hours. In general, the similarity of results obtained after levulose and after artichokes is striking.

It must be remembered that one-fifth the available carbohydrate in these artichokes was dextrose. The amounts of dextrose given varied between 13 and 20 gm. in the different experiments. Possibly this was better utilized by reason of slower absorption.

EFFECT OF INULIN ON THE METABOLISM OF DIABETIC PATIENTS

The effect of inulin on the metabolism of three normal subjects and two diabetic patients is shown in Table 5. In the instance of the three normal subjects, two females and one male, a difference in the results appears. The first two patients, Cases 10 and 11, showed very slight increases in respiratory quotients but fairly definite increases in heat production through the six hours. In Case 10, intestinal fermentation was noticed about three hours after the inulin was taken, and inulin was recovered in the stools eight hours later. In Case 12, a marked rise in respiratory quotient occurred during the second half-hour which also was found persisting during the fifth half-hour. It is true that she seemed a little nervous, but she had practiced wearing the mask for the metabolism determination the day before and was a very intelligent and cooperative dietitian. The results represent averages of six periods in all of which the quotients were between 0.90 and 0.93. It is very difficult to justify the exclusion of these results. That such variations in pure inulin, due to varying degrees of hydrolysis in the stomach, are to be expected, was the opinion of Lewis. Furthermore, other factors, such as the character of the bacterial flora, might be expected to affect

TABLE 5.—*Effect of Inulin, 1.5 Gm. per Kilogram, on Metabolism of Three Normal and Two Diabetic Subjects*

Case	Amount Given, Gm.	Weight of Patient Above or Below Standard, per Cent.	Variation of Basal Metabolism from Standard (H. & B.), per Cent.		Basal	Half-Hours After Ingestion 1	2	3	4	5	6	7	8	9	10	11	12
10 (normal).....	105	—1	—1	Respiratory quotient	0.80	....	0.80	....	0.81	....	....	....	0.80	....	....	....	0.79
				Calories per 24 hours	1,598	....	1,777	....	1,781	....	....	....	1,797	....	....	....	1,786
				Percentage deviation from basal	....	....	+4	....	+4	....	....	....	+5	....	....	....	+5
11 (normal).....	92	±0	—12	Respiratory quotient	0.80	....	0.79	....	....	0.81	....	....	....	0.83	....	....	0.79
				Calories per 24 hours	1,258	....	1,310	....	....	1,282	....	....	....	1,331	....	....	1,345
				Percentage deviation from basal	....	....	+4	....	....	+2	....	....	....	+6	....	....	+7
12 (normal).....	60	—36	+12	Respiratory quotient	0.83	....	0.91	....	....	0.91	....	....	....	0.82	....	....	0.83
				Calories per 24 hours	1,370	....	1,294	....	....	1,265	....	....	....	1,265	....	....	1,282
				Percentage deviation from basal	....	....	—5	....	....	—7	....	....	....	—7	....	....	—6
13 (diabetic).....	90	—5	—4	Respiratory quotient	0.77	....	0.77	....	0.76	....	0.74	....	....	....	0.77	....	0.78
				Calories per 24 hours	1,550	....	1,605	....	1,547	....	1,464	....	....	....	1,544	....	1,685*
				Percentage deviation from basal	....	....	+6	....	±0	....	—6	....	....	....	—0.4	....	+9
14 (diabetic).....	90	—15	—8	Respiratory quotient	0.77	....	0.77†	....	0.78	....	0.77	....	....	....	0.76	....	....
				Calories per 24 hours	1,379	....	1,420	....	1,403	....	1,475	....	....	....	1,321	....	....
				Percentage deviation from basal	....	....	+3	....	+2	....	+7	....	....	....	—4	....	....

* Restless. † Maximum, 82.

the absorption of split products of inulin. The three normal subjects exhibited slight increases in respiratory quotient and, in two of the cases, increases in heat production occurred. The fact that the respiratory quotients and metabolism were not below the initial levels at the end of the six hours may be taken as evidence that absorption of some food had occurred. With the two diabetic patients, the case is somewhat different. Both cases were severe. Patient 13 had just recovered from a period of severe acidosis, and was restless during the sixth hour. During the third hour, drowsiness may account for the fall in respiratory quotients. Patient 14 had a single quotient of 0.82 during the second half-hour, but the average quotients during this half-hour did not exceed the basal quotient. In both patients, a slight increase in heat production occurred, but the experiments do not otherwise give evidences of absorption of inulin.

TABLE 6.—*Effect of Inulin, Levulose and Artichokes on the Blood Sugar*

Case	Substance Given	Amount Carbohydrate, Gm.	Fasting	Hours After Ingestion 1	2	3	4	5	6
12 (normal)	Inulin	60	0.09	....	0.08	....	....	....	0.08
13 (normal)	Inulin	92	0.08	....	0.08	....	....	....	0.05
10 (normal)	Inulin	105	0.10	0.10	....	0.09	....	....	0.10
14 Diabetic	Inulin	90	0.20	0.21	....	0.22	....	0.17	....
15 Diabetic	Inulin	90	0.30	....	0.31	0.28	....	....	0.23
7 Diabetic	Levulose	50.6	0.07	....	0.08	....	0.09	....	0.09
8 Diabetic	Levulose	87.0	0.33	....	0.44	....	....	....	0.30
5 Diabetic	Levulose	48.0	0.24	0.31	....	0.33	....	....	0.24
6 Diabetic	Levulose	72.0*	0.16	0.17	....	0.27	....	0.28	0.24
9 Diabetic	Levulose	50.0†	0.17	0.16	....	....	0.22	....	0.25
1 Diabetic	Artichokes	71.0	0.25	....	0.30	....	....	....	0.21
2 Diabetic	Artichokes	79.0	0.19	0.27	....	0.24	....	....	0.17
3 Diabetic	Artichokes	37.0	0.26	....	....	0.29	....	....	0.23
4 Diabetic	Artichokes	51.0	0.17	....	0.19	0.17	....	....	0.13
5 Diabetic	Artichokes	81.0	0.31	0.33	....	0.29	....	....	0.20
6 Diabetic	Artichokes	53.0	0.19	0.22	....	0.26	....	....	0.24

* Levulose given, 12 gm. an hour.
† Levulose given, 10 gm. an hour.

BLOOD SUGAR, AS AFFECTED BY ARTICHOKES, INULIN AND LEVULOSE

The changes in blood sugar percentages after the administration of inulin, levulose and artichokes are shown in Table 6. Inulin produced no significant increase in either the normal or the diabetic subjects. With levulose the facts are quite different. With the exception of the remarkable Case 7, in which the patient showed almost no change in the blood sugar level after taking 1.5 gm. of levulose per kilogram of body weight, levulose produced a distinct rise in the percentage of blood sugar of diabetic patients, whether taken in a single large dose or as small amounts at hourly intervals. In the latter instance, the increase in the blood sugar tended to be progressive so long as levulose was taken. When baked artichokes were given to diabetic patients, a slight rise in blood sugar was observed in every instance, with a fall at the end of the six

hours to values slightly lower than the initial value. In two cases, we are able to compare in the same subject the results with levulose and with artichokes. With Case 1, the increase in blood sugar was 0.05 when 71 gm. of carbohydrate in the form of baked artichokes was given, whereas, when 48 gm. of pure levulose was taken, the increase during the first hour was 0.07. At the end of six hours after artichokes, the blood sugar was below the initial level, whereas it was the same as the initial level in the levulose test. In Case 1, the increase in respiratory quotient was greater with artichokes and more prolonged than with the levulose. With Case 6, a comparison is possible between the effect on the blood sugar of levulose taken in hourly doses and artichokes. The greater increase in the blood sugars occurred after the levulose. In

TABLE 7.—*Effect of Inulin Obtained from Dahlia Bulbs on the Sugar of the Blood and Urine Before and After Hydrolysis*

		Blood Sugar per 100 C.c.			Corpuscles, per Cent. by Volume	Urine		
Subject	Time	Whole Blood, Mg.	Plasma, Mg.	Corpuscles, Mg.		Volume per Hour, C.c.	Sugar per Hour, Mg.	Remarks
15	8:06	109+6	117+1	.....	..	...	.....	
(Normal)	8:27	.....	.....	.....	..	38	.....	Fasting
Weight, 57 kg.	8:35	Inulin, 95 gm. in 500 c.c. of water						
Age, 26	9:35	109+6	107+4	.....	..	53	.....	
	10:43	109+0	105+7	.....	..	131	.....	
	2:35	101+6	98+3	.....	..	9	.....	
						27	121+1	Fasting
16	8:30	.....	.....	.....	..			
(Diabetic)	8:53	283+7	270+0	234+20	35	...	.....	
	9:15	Inulin, 70 gm. in 600 c.c. of water						
	9:50	.....	.....	.....	..	42	252+4	
	10:32	265+13	267+9	253+22	28	...	.....	
	10:47	.....	.....	.....	..	142	415+0	
	11:18	282+4	280+2	286+8	30	...	.....	
	11:50	.....	.....	.....	..	200	513+0	
	3:34	231+7	238+7	218+7	31	..	.....	
	3:42	.....	.....	.....	..	75	162+3	

both cases, high quotients were obtained at the end of the period. These results with the respiratory quotient showed that: (1) the inulin used was not absorbed, or was absorbed unchanged, or was absorbed too slowly to affect the blood sugar; (2) baked artichokes did not increase the blood sugar as much as pure levulose in equivalent amounts; (3) when levulose was given in small divided doses, the effect on the blood sugar was similar to that in the experiments in which artichokes were taken, but a greater increase was found, and (4) the absorption of some reducing sugar, after the taking of artichokes was proved.

Inulin made no change in the urinary sugar excretion, with the possible exception of in Case 13, a case of severe diabetes in which sugar excretion may have increased for another reason, namely, the omission of insulin on that day. One diabetic patient excreted no sugar after either levulose or artichokes. One patient excreted no sugar after levulose, and another was sugar-free during the six hours after taking

artichokes. The others showed definite increases in glycosuria after both levulose and artichokes. Levulose was not found in the urine by the Seliwanoff test. Patient 1 excreted 8.5 gm. of sugar in six hours after 48 gm. of levulose, and only 9.2 gm. of sugar after 71 gm. of carbohydrate in the form of baked artichokes.

ABSORPTION OF INULIN

Two experiments were carried on to determine whether there was any evidence of the absorption of inulin as such or of some polymer of levulose. The method employed was to give inulin by mouth and at intervals to determine the venous blood sugar before and after hydrolysis of the Folin filtrate. For this purpose it was found that two drops of the 1 per cent. hydrochloric acid, when added to 2 c. c. of the Folin filtrate and set in a boiling water bath for two hours, would hydrolize inulin without causing destruction of the glucose normally present. Stronger solutions of hydrochloric acid, such as 10 per cent., could not be usel since they caused destruction of the glucose as well as hydrolysis of inulin. The added acid was then neutralized with 2 drops of a sodium hydroxid solution, which was equivalent to the hydrochloric acid. Similarly, the sugar in the urine was determined before and after hydrolysis by the method of Folin. In Table 7 are shown the results. It is seen that, with the normal subject, the difference value, i. e., the increase in reducing power of the Folin filtrate as hydrolized with hydrochloric acid, increased somewhat after the taking of inulin. However, we were unable to get a Seliwanoff test. In the case of the diabetic subject, there was a considerable increase in the difference value in the urinary excretion found, but in neither case could a Seliwanoff reaction be obtained. These results are suggestive but not conclusive. It is to be remembered that the blood specimens were venous blood, and hence it is possible that absorbed inulin was held in the liver and merely displaced dextrin-like substances. Another possibility is that it was taken up by the tissues. In either case, it would not be demonstrable in the venous blood.

INULIN IN THE PREVENTION OF ACIDOSIS

The tendency toward the development of acidosis, which might have been produced by the withdrawal of insulin on the experiment days, was apparently counteracted by all three substances. The plasma carbon dioxid combining power remained practically constant during the six hours of the inulin tests, increased by 1.9 per cent. by volume during the levulose experiments, and, in the experiments with artichokes, increased from an average of 56.8 per cent. by volume fasting to 57.7 per cent. by volume at the end of six hours.

In two instances, acidosis was present when the artichokes were taken. The fasting urine specimen of Case 5 gave a + + + + ferric chlorid test and the plasma carbon dioxid combining power was only 44.3 per cent. by volume. The fasting urine of Case 3 gave a + + ferric chlorid test. In the first instance, the respiratory quotient rose from 0.73 to 0.78; the heat production increased by 11 per cent., and the plasma bicarbonate increased by 1 per cent. by volume during the two hours following ingestion of artichokes. In the second case, a rise of 0.07 in the respiratory quotient and an increase of 2 per cent. by volume in the plasma bicarbonate occurred during the third hour. Thus, the beneficial effects of artichokes on diabetic acidosis were clearly suggested.

TABLE 8.—*Alterations in Plasma Cholesterol*

			Milligrams per 100 C.c.			
				Hours After Ingestion		
Carbohydrate	Case	Grams per Kg.	Fasting	1	2	6
Inulin	Normal 10	1.3	96.3	97.7	124	159
	Normal 11	1.5	114	...	151	155
	Normal 12	1.3	116	112	...	106
Inulin	13	1.5	112	161	188	117
	14	1.5	426	452	452	469
Levulose	7	1.6	114	106	95.7	102
	8	1.6	122	...	110	116
	1	1.2	152	126	120	102
	9	1.3	96.3	106	116	101
	6	1.1	217	227	231	189
Artichokes	1	1.8	135	188	...	210
	2	1.4	120	145	140	114
	3	0.7	109	...	115	134
	4	0.9	63.4	65.2	81.6	...
	5	1.5	102	104	141	169
	6	1.2	215	147	169	194

BLOOD LIPOIDS, AS AFFECTED BY ARTICHOKES, INULIN AND LEVULOSE

In Tables 8 to 11 are given analyses of the plasma lipoids, for which we are indebted to Prof. W. R. Bloor of the University of Rochester Medical School and the Robinson Foundation.

Temporary increases in the blood lipoids are observed after fat feeding, starvation, narcosis and hemorrhage. In any lipemia, increases occur in the fatty acid, lecithin and cholesterol, although the latter is inconstant in alimentary lipemia. The rate of fat absorption and the rate of disappearance from the blood control alimentary lipemia. Bloor [29] considers that diabetic lipemia is due to the lack of hormone aiding in the removal of fat, an hypothesis apparently confirmed by the discovery of insulin. We have observed that insulin prevents the increase both in the blood sugar and the blood lipoids which follows the taking of levulose by a diabetic patient.

29. Bloor, W. R.: J. Biol. Chem. **49**:20, 1921.

In seeking to explain the changes in plasma lipoids in these experiments, three possible sources must be considered: (1) the food; (2) the fat depots of the body, and (3) the synthesis from other constituents of the body. The mechanism of synthesis of blood lipoids from other constituents of the body or diet is entirely unknown, according to Bloor. The influence of fasting and the consequent drain of fat stores on the plasma lipoids is difficult to evaluate in these experiments. In fasting, the blood sugar falls and the blood fat increases. In the experiments with levulose and artichokes, though not with inulin, however, the blood sugar of diabetic patients rose either during the first two hours or throughout the six hours. This fact shows clearly that the

TABLE 9.—*Alterations in Plasma Fatty Acid*

Carbohydrate	Case	Grams per Kg.	Milligrams per 100 C.c.			
			Fasting	Hours After Ingestion		
				1	2	6
Inulin	Normal 10	1.3	356	406	356	346
	Normal 11	1.5	332	...	314	328
	Normal 12	1.3	246	252	...	356
Inulin	13	1.5	446	507	570	453
	14	1.5	482	540	622	697
Levulose	7	1.6	332	324	338	320
	8	1.6	645	...	657	606
	1	1.2	393	413	428	442
	9	1.3	400	388	402	324
	6	1.1	348	623	673	643
Artichokes	1	1.8	402	435	...	522
	2	1.4	392	417	374	422
	3	0.7	398	...	448	448
	4	0.9	444	358	456	...
	5	1.5	422	440	480	536
	6	1.2	667	623	456	450

results are not to be regarded as entirely due to fasting and nonabsorption of the substances fed. Furthermore, the subjects of levulose and artichoke experiments received amounts sufficient on the average for their caloric needs, during the period of the test. Another factor that may have influenced the results was the withdrawal of insulin. All but one of the diabetic subjects had been receiving insulin. None had been given for at least sixteen hours prior to the experiments. Only one patient, Case 5, had received as much as 30 units a day. It is unlikely that its withdrawal could have greatly affected the experimental results. We feel that the substances fed must be regarded as of chief importance in producing the observed changes.

In discussing the alterations in plasma lipoids, we shall consider each separately. Significant increases in the cholesterol of the plasma occurred in twelve of sixteen experiments. In eight instances, the maximum was reached at six hours and, in the other four cases, during the first two hours. The increases occurred in both normal

and diabetic subjects and in all four types of experiment. The four subjects, one normal, Case 11, and three diabetic, who did not exhibit an increase in plasma cholesterol, were distinguished from the ten who did, first, by their weight and, second, by the behavior of their respiratory quotients. Their average weight was 29 per cent. below standard, and their average maximal increase in respiratory quotient during the experiments was 0.095. The average weight of the ten subjects was 11 per cent. below standard, and the average maximal increase in respiratory quotient during the ten experiments was 0.04. In Cases 1 and 6, two experiments each were done. Patient 6 exhibited an increase in cholesterol when levulose was given in five hourly doses of 10 gm., but not when artichokes equivalent to 53 gm. of carbohydrate

TABLE 10.—*Alterations in Plasma Lecithin*

			Milligrams per 100 C.c.			
				Hours After Ingestion		
Carbohydrate	Case	Grams per Kg.	Fasting	1	2	6
Inulin	Normal 10	1.3	132	157	182	186
	Normal 11	1.5	270	...	274	282
	Normal 12	1.3	158	198	...	199
Inulin	13	1.5	265	278	262	268
	14	1.5	537	541	570	515
Levulose	7	1.6	194	182	258	229
	8	1.6	262	...	271	286
	1	1.2	316	502	449	326
	9	1.3	230	227	381	379
	6	1.1	269	194	334	389
Artichokes	1	1.8	331	188	...	260
	2	1.4	438	369	336	240
	3	0.7	274	...	294	299
	4	0.9	252	243	243	...
	5	1.5	350	285	302	272
	6	1.2	370	252	234	234

were taken. The more rapid absorption of pure levulose, as compared with artichokes, may have brought about this result. This suggests that the tendency for an increase in the plasma cholesterol to occur after the ingestion of carbohydrates is dependent on the character of the metabolism thereby induced and on the preceding nutritional state. The lower the weight and the greater the increase in respiratory quotient, the less will be the increase in plasma cholesterol, or the better the utilization of carbohydrate, the less will be the tendency for an increase in cholesterol.

The initial level of the blood sugar and of the cholesterol seemed not to affect the increase. The severity of the diabetes seemed to be a factor. Thus Cases 7, 8 and 6, who had little or no increase in plasma cholesterol, were milder than the other diabetic cases.

The alterations in the fatty acids of the plasma paralleled fairly closely those of the cholesterol. Increases occurred in thirteen experiments, the

highest values being observed in the sixth hour in seven cases, and in the second hour in five cases. The parellelism was not exact, however, for, in five instances, an increase in one lipoid was not accompanied by an increase in the other. Furthermore, in only six cases, the maximal value for cholesterol occurred at the same time as that for fatty acid. Nevertheless, the outstanding fact is that, in thirteen experiments, an average maximal increase of 24.6 per cent. occurred during the six hours. While it is true that the three patients who showed no increase were 27 per cent. underweight, two patients who showed marked increases also were 39 per cent. and 26 per cent., respectively, underweight. It is difficult to correlate this increase with any other factors.

Lecithin, like cholesterol, is found in all living body cells. It increases with the fatty acids in any lipemia, although usually more

TABLE 11.—*Alterations in Plasma Free Fat*

			Milligrams per 100 C.c.			
				Hours After Ingestion		
Carbohydrate	Case	Grams per Kg.	Fasting	1	2	6
Inulin	Normal 10	1.3	226	269	193	171
	Normal 11	1.5	114	...	82	88
	Normal 12	1.3	101	83	...	189
Inulin	13	1.5	273	267	333	276
	14	1.5	−34	29	91	187
Levulose	7	1.6	164	167	134	134
	8	1.6	430	...	446	477
	1	1.2	−12	35	89	160
	9	1.3	214	201	169	18
	6	1.1	98	417	374	320
Artichokes	1	1.8	137	247	...	258
	2	1.4	60	163	163	224
	3	0.7	180	...	214	209
	4	0.9	209	174	267	...
	5	1.5	154	215	241	218
	6	1.2	349	406	244	229

slowly, and the increase is of longer duration, according to Bloor. It is synthesized from fat and phosphoric acid, and probably represents one state in fat metabolism. Bloor [30] found a relatively large part of the unsaturated fatty acids of the blood in combinations with cholesterol and a smaller portion combined as phospholipoid. The lecithin findings are not complete, but if it contains one saturated and one unsaturated acid, the latter is probably the same as that of the liver, and relation between blood and liver lecithin must exist. This work tends to support the belief that lecithin represents a means of transportation for fat.

Increases in plasma lecithin occurred in eleven of these experiments. The maximal increase occurred five times in the sixth hour and four times in the second. The average maximal increase was 26.3 per cent.

30. Bloor, W. R.: J. Biol. Chem. **59**:543 (April) 1924.

Increases in free fat were found in thirteen experiments. If the levulose experiments with Case 1 are omitted from the average, the average maximal increase in free fat was 155 per cent. The alterations in plasma fat occurred more promptly and were greater in degree than those observed with the other lipoids.

The interpretation of these puzzling results must await further study and the criticism of other workers. Striking increases in plasma lipoids were observed in the three normal subjects who received only inulin. Patient 11, whose blood sugar fell to 0.05 per cent. at the end of six hours, showed an increase in plasma lecithin and cholesterol, but a decrease in fatty acids and free fat. This suggests that the withdrawal of fat from the blood may stimulate the formation of lecithin and cholesterol.

Levulose and artichokes produced, in the diabetic subjects, a lipoidemia characterized by a tendency toward an earlier and more marked increase in plasma fat and fatty acid. The higher the initial

TABLE 12.—*Average Diet, Insulin and Weight of Diabetic Patients Taking Artichokes*

Number of Cases	Carbohydrate Added as Artichokes, Gm.	Time, Mo.	Diet at Beginning: Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Diet* at End: Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Insulin: Beginning, Units	Insulin: End, Units	Weight: Beginning, Kg.	Weight: End, Kg.
17	19	6	51	51	105	1,358	59	53	117	1,501	18	21	50.3	42.4

* Exclusive of artichokes.

lipoid values, the less was the tendency for such an increase to occur. In the milder diabetics, little or no increase was observed. This may be explained on the ground that, in the latter, the block in the pathway of carbohydrate utilization is but slight whereas, in the more severe cases with more complete block in the pathway, the carbohydrate may be converted in part into fat. In the most severe cases, even this expedient fails. Possibly this explanation may be invoked in a comparison of Patients 9 and 6, who received small amounts of levulose hourly. In the first, moderate increases in cholesterol and lecithin with a pronounced fall in plasma fat occurred, while the respiratory quotient was scarcely affected and the urine contained sugar. We may infer that practically no increased combustion of carbohydrate and no conversion into fat occurred. In the second, a marked increase in lipoids, with slight glycosuria, and an extraordinary rise in respiratory quotient suggest that conversion of levulose into fat had occurred.

A comparison of the effects of levulose and artichokes on the plasma lipoids may be made in general terms. In Case 1, slightly greater lipoidemia occurred with 71 gm. of carbohydrate, as artichokes, than with

48 gm. of levulose. In Case 6, a decrease in lipoids occurred with 53 gm. of carbohydrate in the form of artichokes, as compared with an increase in lipoids when 50 gm. of levulose were given in divided doses. In general, the slower absorption of carbohydrate with a more prolonged rise in respiratory quotient when artichokes were given caused a less pronounced lipoidemia than did pure levulose.

JERUSALEM ARTICHOKES IN THE DIET

The Jerusalem artichoke tuber resembles the potato in appearance, and is easily obtained in large markets. It may be prepared for use as food in a variety of ways, such as boiling, baking or frying. It must be remembered, however, that if the artichoke is boiled a large part of the inulin will be lost in the water. In one experiment, 43 per cent. of the inulin was recovered from the water in which the artichokes were boiled. Baking is the best method of cooking. Mrs. Leatherbee, who has served artichokes to many patients in her boarding house for diabetic patients, recommends the following recipe:

> The artichokes should be washed in cold water and sliced like cucumbers, then baked in a small casserole till soft. No water should be added, but mineral oil may be used.

The artichokes baked in their skins resemble baked potatoes in appearance but have a very sweet taste. Thirty minutes' baking will drive off enough water to cause a loss of 65 per cent. in weight. Hence, the carbohydrate value must be calculated from their weight before cooking. As to the changes that occur in the carbohydrate of the artichokes during baking, we are uncertain. The inulin of artichokes is more easily hydrolyzed than that of dahlia tubers. During baking, the slow rise of temperature in the center of the artichokes gives opportunity for rapid hydrolysis before the inulase is destroyed. The content of levulose or of easily hydrolyzed levulosans may be increased, although we have been unable to demonstrate it. At any rate, the baked artichokes are more palatable than the boiled and are eagerly taken, either regularly or at intervals, by the diabetic patients.

Twenty-five diabetic patients have taken artichokes in addition to their regular diet (or occasionally in substitution for 5 per cent. vegetables) for periods varying from a few days to fifteen months. In some cases, the artichokes were taken daily, in others, on alternate days, and, in one instance, only once a week. The average amount of uncooked artichokes taken in a day was 130 gm. In Table 12 are given the average results for seventeen patients who took artichokes for at least one month. These patients all showed improvement during the test. Needless to say, this improvement is not ascribed to the artichokes alone, but the most conservative will agree that they did

no harm. In all cases, the patients were able to eat artichokes in these moderate amounts without increasing glycosuria, when present, or producing glycosuria when it was previously absent.

Artichokes may occasionally be used to render the urine sugar free without increasing the insulin dose or decreasing the diet. Patient 15, a boy, aged 7 years, became sugar free when 100 gm. of baked artichokes was substituted for 15 gm. of carbohydrate, as orange and Triscuit. Patient 16, a woman, took baked artichokes in place of 5 per cent. vegetables and fruit for two days. Although she thus increased the carbohydrate of her diet by 10 gm., she became sugar free. To confirm this result she returned the next day to her previous diet and glycosuria reappeared. No inulin or levulose was found in the stools of patients who received moderate amounts of artichokes.

The addition of artichokes to the diet apparently makes it possible to add other food too. Thus, these seventeen patients increased the total calories of their diets by 11 per cent. besides the artichokes, although the insulin dosage was increased by only 3 units. This is understandable if one considers the unusual readiness with which levulose favors glycogen formation. Helly [31] has shown that, even in depancreatized dogs, glycogen may be deposited in the liver when levulose is given. It may well be that the good effects of artichokes are due to the slow absorption of levulose, increased glycogen formation and consequent improvement of tolerance of the patient and his protection against acidosis.

CONCLUSIONS

Clinically, the use of Jerusalem artichokes proved beneficial to a group of diabetic patients who used them for average periods of six months. In the amounts given, they were added to the diet without increasing glycosuria or producing it where previously absent, and when substituted for other carbohydrates in the diet, in certain instances, they rendered the urine sugar free. During the periods of these tests, patients were able to increase the other components of the diet and to gain weight with only a slight addition to their insulin dosage.

Experimentally, the advantages of artichokes seemed to depend on the gradual liberation and slow absorption of levulose, although a small amount of glucose also was present. Baked artichokes raised the respiratory quotient in all cases, including cases with acidosis.

The increase in the respiratory quotient tended to occur later and to be more prolonged than with levulose.

The increase in blood sugar produced by artichokes was definite but less than that produced by an equivalent amount of carbohydrate in the form of levulose.

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31. Helly: Ztschr. f. exper. Path. u. Therap. **15**:464, 1914.

Experiments conducted in order to make comparison with inulin derived from dahlia tubers showed that inulin did not cause a significant rise in blood sugar percentage but that it had a slight though definite effect on the respiratory quotient and metabolism.

Increases in the lipoids of the plasma resulted when artichokes and inulin, as well as levulose, were given patients. The greatest increases occurred in the more severe diabetic subjects when levulose was given. In subjects receiving both levulose and artichokes on different occasions, the latter provoked the lesser degree of lipoidemia.

HYPOGLYCEMIA *

REPORT OF A CASE UNASSOCIATED WITH INSULIN ADMINISTRATION

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The clinical history of a case in which hypoglycemia was associated with symptoms very similar to those occurring in the hypoglycemic shock following overdosage with insulin is here given.

REPORT OF CASE

H. F. C., a Chinese man, aged 33, was admited to the Peking Union Medical College Hospital, Aug. 17, 1924, for gastric analysis and roentgen-ray examination of the gastro-intestinal tract, on account of epigastric distress and feeling of flatulence after meals. The past history was irrelevant, except that he never had any previous attacks in any way resembling that described below, nor any symptoms suggestive of hysteria.

Shortly after admission, the patient developed a diarrhea which lasted for five or six days, three or four stools daily with abdominal cramps. The stools were liquid and fecal, with mucus, but contained no blood. The night before the colon examination, the supper was omitted and he was given 40 c.c. of castor oil, which produced a number of liquid bowel movements. The next morning, without breakfast, a soapsuds enema was given. Immediately after the enema, the patient had very severe, cramplike pains in the abdomen. He had speech difficulty and was disoriented. The hands and feet were held in spasm resembling the carpopedal spasm of tetany, but no facial phenomenon (Chvostek's sign) was obtainable. The abdominal muscles were rigid. The whole body was in active tremor, the face pale and dripping with profuse cold perspiration, and the pulse weak and rapid, giving a picture of severe shock. During the attack, the patient felt numb and stiff in the face, as well as in the extremities, which could be moved only with difficulty; but there was no blurring of vision, tinnitus or loss of consciousness. The abdominal cramps lasted for an hour, but the spasm of hands and feet did not disappear for two and one-half hours. The picture, clinically, in every way resembled a moderately severe hypoglycemic (insulin) shock, although at the time the possibility of hysteria was also considered.

The colon examination was postponed until two days later when exactly the same preparation was given, in an attempt to reproduce the same syndrome, but without result. During this time, however, the diarrhea had ceased and food in normal quantities had been taken.

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* From the chemical laboratory, the department of medicine, Peking Union Medical College.

On the assumption that the rigidity of the hands and feet might be due to tetany, blood was taken for calcium and phosphorus determination.[1] The results of the blood examination made during the attack and on the second day following are given in the accompanying table.

Blood Examination

	Mg. per 100 C.c. Glucose	Mg. per 100 C.c. Calcium	Mg. per 100 C.c. Inorganic Phosphorus	Percentage by Volume Carbon Dioxid Capacity
Aug. 25, 1924, without attack....	75	11.3	1.7	50.4
Aug. 25, 1924, without attack...	100	....	3.8	55.1

The value for calcium was found to be high, while that for phosphorus was very low. The high calcium and normal carbon dioxid capacity, together with the absence of the facial phenomenon, rendered the diagnosis of tetany quite unlikely. Furthermore, the low phosphorus in the blood led one to anticipate a low blood sugar, as the associated presence of these phenomena has been shown [2] to occur during the process of active insulin action. Banting, Campbell and Fletcher [3] have described hypoglycemic shock following insulin injections. When the level of the blood sugar gets as low as 0.075 per cent., patients experience hunger and a feeling of fatigue, accompanied by vasomotor phenomena and tremulous sensations. The blood sugar determined in this case was 0.075 per cent. On account of the hypoglycemia present and the similarity of the symptoms manifested in this case to the hypoglycemic syndrome, one is strongly led to assume that this patient was suffering from a condition analogous to hypoglycemic shock.

We are unable to offer a certain explanation of the etiology of this attack. The writers have not found reports of any similar case in which the blood sugar has been studied. But the facts are that this man had a severe and dehydrating diarrhea, and had been vigorously purged and partially starved before the attack occurred. We think it not unlikely that the depletion of carbohydrate from a susceptible patient by an exhausting diarrhea, fasting and severe purging may sufficiently lower the blood sugar to cause the symptoms of hypoglycemic shock, when given some immediate stimulus (here the manipulations necessary to give an enema) to set them off.

1. The chemical methods employed were: (*a*) Glucose: Folin, O., and Wu, H.: J. Biol. Chem. **38**:81 (May) 1919. (*b*) Calcium: Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921. (*c*) Phosphorus: Briggs, A. P.: J. Biol. Chem. **53**:13 (July) 1922. (*d*) Carbon dioxid combining power: Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:289 (June) 1917.

2. Harrop, G. A., Jr., and Benedict, E. M.: J. Biol. Chem. **59**:683 (April) 1924.

3. Banting, F. G.; Campbell, W. R., and Fletcher, A. A.: Brit. M. J. **1**:8 (Jan. 6) 1923.

In conclusion, it is desired to call attention to the possibility of hypoglycemic shock, after such a train of events, in a predisposed subject. Before the discovery of insulin, the syndrome of hypoglycemic shock was unknown and unrecognized, and many hysterical attacks, so considered, might prove in reality to be hypoglycemic in nature, if blood sugar determinations were made. In cases of cholera, in which the muscular cramps have usually been ascribed to dehydration, estimations of blood sugar would be interesting, in order to determine whether or not hypoglycemia may play a part in their causation.

Book Reviews

LECTURES ON PATHOLOGY. By LUDWIG ASCHOFF, M.D., Professor of Pathologic Anatomy, University of Freiburg. Delivered in the United States, 1924. Thirty-Five Illustrations.

This book contains a number of lectures that were delivered by Professor Aschoff, during his recent visit to the United States. It includes, among others, the Lane Lectures of Leland Stanford University, the Janeway Lectures of the Mount Sinai Hospital, New York, and the Osler Memorial and the Harvey Lectures.

Altogether there are fourteen separate papers. The subjects discussed are varied; they cover a wide range of pathologic data and evidently are not intended to form a consistent series. All, however, are concerned with subjects vital to medicine at the present time. Among these subjects, one finds the following: the reticulo-endothelial system; the pathogenesis of human pulmonary consumption; concept of inflammation; pathologic fatty changes; the normal and pathologic morphology of the suprarenals; atherosclerosis; ovulation and menstruation; the orthology and pathology of the extrahepatic passages; the site of formation of bile pigment; thrombosis; the relation of mucosal erosions to the development of ulcers of the stomach; the goiter problem, especially the goiter of puberty; renal secretions, and renal diseases.

It is impossible, in this review, to give a resumé or even to state the main conclusions of the author. On all these problems, he has worked and written for years, and these lectures are really condensations of his numerous papers and monographs. For that reason, many physicians will find this book most useful in obtaining fairly concise statements of Aschoff's voluminous writings.

Of greatest interest, probably, are his discussions of the reticulo-endothelial system and the pathogenesis of human pulmonary consumption. More especially, Aschoff discusses, in connection with the reticulo-endothelial system, the morphology and origin of its elements, and then takes up the reaction of these cells in various pathologic processes, laying stress particularly on their relation to blood destruction, to bile pigment production, to their participation in general metabolic functions, such as the metabolism of fat, the metabolism of proteins, and their relation to the storage and metabolism of iron. Of particular interest, too, is his discussion of this system in relation to defense reactions and ferment production.

Aschoff presents concisely his well known views on pulmonary tuberculosis, emphasizing the importance of recognizing a primary infectious stage, characterized by an exudative, rapidly caseating bronchopneumonia, which is usually single. There may be a reinfection, which is usually multiple; this often occurs at the apex of the lung and results commonly in a process of cicatrization and contraction, this forming the productive type of phthisis.

His concept of inflammation is founded on a broad biologic basis. He analyzes in detail the various factors entering into this process, and presents an interesting but exceedingly complex tabular representation of the inflammatory reactions.

Aschoff emphasizes the complexity of the process of thrombosis and discusses several factors in the formation of thrombi. He takes up so-called spontaneous thrombosis, presenting in a masterly way its morphology and the mechanics of its formation. This chapter is recommended especially to the surgeon for his careful consideration.

Attention is called to the interesting chapter on mucosal erosions. Here appear many statements bearing on the origin and prevention of ulcers of the stomach.

To those interested in the study of goiter, his morphologic discussion of the problem will be of interest. He also draws many comparisons between the disease as it appears in Europe and in this country.

The author has a wide range of detailed information not only in the field of morphology, where he stands supreme, but also in biochemistry, bacteriology, immunity, and especially in comparative pathology. From all these sources, he utilizes and correlates important data in the elucidation of disease processes.

THE PHYSIOLOGY OF EXERCISE. A TEXTBOOK FOR STUDENTS OF PHYSICAL EDUCATION. By JAMES HUFF MCCURDY, A.M., M.D., M.P.E., Director of Physical Education Course in the International Young Men's Christian Association College, Springfield, Mass.; Editor of the American Physical Education Review. Illustrated. Pp. 242. Philadelphia: Lea and Febiger, 1924.

This book was written to serve as a guide and text for students and teachers of physical education, and most of the material presented was obtained through studies carried on over a period of more than twenty years at the International Young Men's Christian Association College at Springfield. There is an extensive bibliography, and frequent references to the literature on the subject are made. It deals largely with the effects of exercise and the various forms of athletic contests on individuals, both in regard to general constitutional effects and to the influence of exercise on the various organs, with particular emphasis on functional changes.